VOL. 1, NO. 3, AUGUST, 1959

human factors

THE JOURNAL OF THE HUMAN FACTORS SOCIETY

Contents

A SURVEY OF RADIOBIOLOGY FOR ENGINEERS 1
Blaine H. Lavedahl

THE INFLUENCE OF CONTROL GAIN IN A FIRST-ORDER MAN-MACHINE CONTROL SYSTEM 69
Clarence L. Tipton and Henry P. Birmingham

OFFICIAL SYSTEM DESIGN AND THE EMPTY FIELD 72
Martin I. Kurke

THE AUTHORS 75

EDITORIAL 77

PERGAMON PRESS NEW YORK • LONDON • PARIS • LOS ANGELES

OFFICERS AND EXECUTIVE COUNCIL

The Human Factors Society is a non-profit California Corporation. The officers and members of the Executive Council are:

PRESIDENT: Renato Contini, 1959
PRESIDENT-ELECT: Arnold M. Small, 1959
VICE PRESIDENT: John Lyman, 1959
SECRETARY: Paul G. Cheatham, 1959
TREASURER: Donald W. Conover, 1959
EDITOR-IN-CHIEF: Stanley Lippert, 1959-1961

EXECUTIVE COUNCIL:
Max W. Lund, 1959-1961
Ross A. McFarland, 1959-1961
Paul M. Fitts, 1959-1960
Jack A. Kraft, 1959-1960
Hans T. E. Hertzberg, 1959
Clifford P. Seitz, 1959

EDITORIAL BOARD:
Walter P. Grether
Blaine H. Levedahl
J. C. R. Licklider
Stanley Lippert
John Lyman
John P. Meehan
Allison K. Simons
Franklin V. Taylor
Neil D. Warren

COPYRIGHT©, 1959
by the HUMAN FACTORS SOCIETY

PUBLISHED BY
PERGAMON PRESS, 122 E. 55th St.,
New York 22, N. Y.

Printed in U.S.A.

Address general correspondence to Human Factors Society, P.O. Box 263, Arlington 10, Virginia, Attention of **Paul G. Cheatham,** Secretary for Society business including payment of dues.

Address matters pertaining to the Journal to **Human Factors,** Department of Engineering, University of California, Los Angeles 24, Calif.

John Lyman, Managing Editor, for Journal or Bulletin Subscriptions or other publication business.

Stanley Lippert, Editor-in-Chief, for submission of articles and letters to the editor.

Address Bulletin news to **Charles W. Simon,** 1030-F Fifth Street, Santa Monica, Calif.

SUBSCRIPTION PRICE, Journal $10.00 (£3:10s.) per year.
Non-members subscriptions to be sent direct to the publisher.
Bulletin, $5.00 per year. Orders to be sent to the Society.
MEMBERSHIP in Society includes subscription to both publications.

A Survey of Radiobiology for Engineers

BLAINE H. LEVEDAHL, Associate Professor of Zoology, University of California, Los Angeles; and Consultant, Douglas Aircraft Company, Inc.

The effect of radiation on biological systems is reviewed. Types of particle and electromagnetic radiation and the mechanisms of absorption and energy dissipation commonly found when radiation interacts with matter are discussed. The effects of radiation on living systems in general are examined. The target theory and the indirect theory of action of radiation are compared in terms of experimental evidence. The major emphasis of the survey is on the consideration of biological effects of radiation on simple systems of single tissue, and on a detailed consideration of radiation effects on the skin, the reproductive system, the circulatory system, and the digestive tract. A summary of permitted tolerance of humans to particulate and electromagnetic radiations is presented .

INTRODUCTION

The problem of the effect of radiation on biological systems is rapidly becoming a subject of paramount interest to all people. Particular interest is, of course, apparent when it is necessary to either design, operate or live with equipment or machines that use nuclear energy as a source of power.

Absolute shielding, that is shielding to protect against all irradiation, is very often impractical. Therefore, all those concerned with nuclear energy as a tool are subjected to what at best is an "educated guess" as to what irradiation is "safe." The "educated guess" is constantly changing as more information becomes available on the biological effects of radiation.

It would seem reasonable, therefore, that if one is concerned with the design of equipment that utilizes nuclear energy, one should have at least a general understanding of two problems:

(1) What theories are there to explain the mechanisms of action of radiation in biological systems and what are the difficulties encountered in establishing these theories as facts, and

(2) What is our present knowledge as to the injurious effects and "safe" limits of radiation in those systems that are vital to the animal?

Knowledge of the first problem may very well allow an intelligent decision to be made for such problems as permitted times, intensities and localization of any inevitable radiation, while knowledge of the second problem would give some reasonable guide to shielding requirements and an understanding of where shielding might most reasonably be sacrificed, if it should become necessary to do so.

Since ultimately man is most interested in man, the principle effort will be directed toward an interpretation of biological effects of radiation in the human animal. In approaching this problem there are a number of points that should be clearly understood. The dose levels at which one may observe some reversible or irreversible effects of radiation in any one animal, system or organism may be quite different in another species of animal, a different system or a different organism. Therefore, in attempting to determine the way in which human tissue is likely to respond to irradiation, there are four courses conceivable:

(1) Experimentation directly on humans. Fortunately, in our society this approach is forbidden in general and limited in practice so that one must

(2) Examine a great variety of different tissues and organisms in a large number of radiobiological experiments. One can then attempt to make certain generalizations from studies on many different species and assume that many will fit reasonably into the same scheme, or

(3) One may attempt to select tissue that apparently has similarity in behavior to human tissue and then undertake a systematic study of the responses of this tissue to radiation under a

[1] This survey is based on reports prepared for the Douglas Aircraft Co., Inc., Santa Monica, California.

EDUCATION LIBRARY

wide variety of physical parameters. The chance of finding such a system is of course very small and similarities of response would be purely accidental.

(4) Additionally, comparative data may be obtained from humans who have been exposed to irradiation for one reason or another and such data may be integrated into the general picture obtained from nonhuman sources.

In what follows, an effort will be made to utilize that information available in the literature for each of the four courses of study mentioned above.

No claim is made to the originality of the concepts presented in these reports. Paraphrasing of good examples of presentation has been employed. The purpose of this article is to bring to engineering personnel a compact presentation of a complex and controversial field with the intent to provide reasonable judgments in areas of design.

TYPES OF RADIATION [19, 36, 48]

The radiations which interest most engineering personnel are those which arise from two broad classes of physical phenomena. First, the engineer concerned with nuclear-powered aircraft must deal with the nuclear instability of atoms that revert to more stable forms. Such transitions release ionizing particles, electromagnetic waves, or both.

Second, electronic equipment engineers must deal with equipment which purposely or incidentally emits electromagnetic energy.

In the first case above, the nucleus of an atom is unstable by virtue of an imbalance of protons and neutrons. In lighter atoms the nucleus is unstable if the ratio of neutrons to protons deviates significantly from one. In heavier atoms the n:p ratio in stable forms may be as high as about 1:2, but ratios greater than this lead to instability. When isotopes are formed by bombardment in a cyclotron, they are apt to contain too many neutrons or too many protons for the nucleus to be stable. In the fission process atoms are broken into smaller fragments. In this case the fission products in general are apt to have an excess of neutrons, the instability may be released by the conversion of a neutron to a proton (n→p) with the emission of a negative beta particle. Should the instability arise from an excess of protons, stability is gained by the conversion of a proton to a neutron (p→n) with the emission of a positive beta particle. These actions can be shown in equation form:

$$n \rightarrow p + \beta^- \text{ and } p \rightarrow n + \beta^+ \xrightarrow{\beta^+ \text{ annihilation } 2\delta}$$

The positive beta particle (positron) is immediately annihilated in a process that gives rise to two quanta of electromagnetic energy (gamma photons). Thus one can see from these equations that both energy and mass are conserved in these reactions.

In the second source of radiation noted above, one observes either x-ray or gamma rays that may be emitted from cathode tubes or from commercial x-ray equipment. While longer wave length electromagnetic radiation is encountered in radar and diathermy, as well as in ultraviolet radiation, they will not be considered in this report.

Particle Radiation

Alpha Particles

When heavy nuclei are concerned in a radioactive decay, there is a distinct tendency for the atoms to throw off a particle made up of two neutrons and two protons. This particle is essentially a nucleus of a helium atom and contains no orbital electrons. Such a particle is called an alpha (α) particle. When an alpha particle is emitted, the nucleus is apt to be left with an excess of neutrons, since, as has been said, lighter elements require relatively fewer neutrons. With an excess of neutrons in the nucleus, there is a further opportunity for a n→p reaction in which there is a further emission of a beta particle. Consequently, alpha particle emission is frequently followed by beta decay.

When light nuclei are involved in radioactive decay, alpha emission is not favored and, indeed, is seldom possible. With light nuclei the most frequent process of radioactive decay is beta decay.

Because alpha particles possess two protons, the net charge is +2. The alpha particle has a mass of 4.0389 mass units and hence is a very large, highly charged particle. Alpha particles have speeds varying from about 1/30 to about 1/10 the velocity of light. The velocity of the particle is, of course, related to the energy levels of the emitting atom. If there is more than one alpha-emitting energy level in an atom, there is then more than one velocity found for the alpha particles.

Because of the heavy mass and double positive charge, alpha particles have tremendous ionizing power. Their large size, however, permits them only slight penetrating power. In air, alpha particles will result in the formation of about 30,000 electron pairs per cm of space traveled. However, alpha particles can be stopped by a sheet of paper, and in biological tissues their range is measured in microns. Hence, they are not able to penetrate the skin and are of little significance as an external radiation peril. If atoms emitting alpha particles become fixed in the body, the problem is quite another one. Here the short-range high-powered particles can be lethal.

Beta Particles

Beta particles are another form of ionizing particle that are released in radioactive decay. Beta particles may be either negatively or positively charged. The negatively charged beta particles are actually electrons and are identical with those from other sources, such as evacuated tubes or heated elements. The essential difference between beta particles and all other electrons lies in relation to their velocity. The energy of beta particles can range all the way from 0 to 3 mev (million electron volts) and sometimes higher. There is one particular difference between beta particles and the alpha particles previously discussed. Instead of having certain discrete energy levels, and hence velocities, the beta particles of nuclear origin form a continuous spectrum of velocities between zero and a maximum value. This apparent violation of quantization has been explained by an energy sharing process that the nuclear beta particle undergoes with the neutrino, during its release from the nucleus. Beta particles of extra-nuclear origin are definitely quantized.

Beta particles show a much greater range and greater penetration than do alpha particles, although they produce only about 75 ion pairs per cm of travel in air. A 3 mev alpha particle has a range of only 1.7 cm in air, whereas a beta particle of similar energy travels 13 m in air. Alpha particles are stopped by 0.06 cm of aluminum, but an energetic beta particle may transverse 1 cm of aluminum. As a result of this penetrating power, beta particles can traverse and damage the skin. Their greatest importance biologically, however, still comes from their being emitted in the body following absorption of a beta-emitting substance.

(a) *Bragg Ionization Effect.*[85] Electrons and other charged particles show a curious variation in ionizing power dependent upon velocity.

If an electron has a velocity, v, 0.4 that of light, c, which corresponds to an energy level of 46,000 ev, it will produce 288 ion pairs per cm of air. As the velocity and energy increase, the amount of ionization decreases so that at a velocity of 0.5 that of light and an energy of 79,000 ev, there are 185 ion pairs produced per cm of air. At v/c=0.8 the energy is 0.34 mev, and 72 ion pairs are produced per cm of air.

The reason for this effect is thought to lie in the assumption that high speed electrons pass atoms too quickly to exert as pronounced an effect as slower electrons.

At extreme speeds and energies there is a slight increase in ionizing ability. This is apparently dependent upon alteration of the electron's electric field with extension of it at right angles to its path, thereby making a wider sweep.

The variation of ionizing power is spoken of as the "Bragg Ionization Effect," and the degree of ionization is called the "specific ionization," K_t. If one wishes to calculate the specific ionization, it is:

$$K_t(\text{ion pairs/cm}) = \frac{46\ (\text{empirical})}{(v/c)^2}$$

where v = velocity of the particle and c = the velocity of light.

Electrons that constitute beta rays are largely from the nucleus, but not entirely. Thos particles associated with the neutrino are definitely of nuclear origin. However, there are those that give discrete energy levels and are associated with K and L x-rays.

Nuclear gamma rays may dislodge K and L electrons, thus producing at once K and L x-rays and electrons of orbital origin at definite energy levels. In producing this effect, the gamma ray may be completely absorbed. This is a phenomenon known as internal conversion.

Neutrons

Since neutrons have no charge, one might at first consider them to be of little or no danger. However, owing to several factors, they are relatively extremely dangerous biologically.

The uncharged nature of the neutron makes it behave very differently in its transit through matter than such particles as electrons, protons, or alpha particles.

Charged particles can exert electric or magnetic forces capable of ionizing the atoms through which they pass. They can also interact with the positively charged nuclei of the atom.

The neutron, however, can experience a force only when it comes within extremely close range of the nucleus. This interaction with the nucleus may be considered as a collision and it may be either elastic or inelastic. This is a general classification and by no means covers all of the ways neutrons interact with matter.

(a) *Elastic Collision.* In the elastic collision the ordinary laws of conversion apply. A portion of the energy from the neutron is transferred to the nucleus in the collision. If the target nucleus is extremely heavy, such as is the case with lead, the energy loss is very small. Light atoms, on the other hand, will, at each collision, naturally reduce the energy of the striking neutron. If this does not make sense at first, consider bouncing a ball against a concrete wall as compared to a blanket.

With this concept, 1 cm of light material such as water will more effectively reduce the intensity of a beam of energetic neutrons than will the same thickness of lead.

(b) *Inelastic Collision—Neutron Capture.* The striking neutron will occasionally enter the nucleus and unite with the other particles, thereby forming a new isotope of the bombarded element. If, as a result, the nucleus is left in an excited state, any excess energy may be carried off by the emission of radiation. The new isotope will obviously have a mass one unit greater than that of the target nucleus. This process is called "neutron capture." The newly formed element may have an atomic weight not existing for that element in its natural state. If this is the case, then the element is bound to be radioactive. Neutrons, because of their mass, which is about that of a proton or hydrogen nucleus, have great kinetic energy and, because they have no charge, penetrate readily into the nuclei. Hydrogen will also capture slow neutrons to form deuterium. Gamma rays are emitted in this process.

In the case of sodium there is often the reaction ${}_{11}Na^{23} + {}_{0}n^{1} = {}_{11}Na^{24}$. This form of sodium is radioactive and emits beta particles.

In the case of nitrogen, ${}_{7}N^{14}$ may become ${}_{6}C^{14}$ by a fast proton being emitted when the nitrogen is struck by a fast neutron. Because of this sort of thing, the effect of neutrons in tissue is greater than one would expect from their comparative ionization figures. The biological effectiveness per particle is rated at from 2 to 10 times as great as that of gamma rays per photon and is sometimes more than this in selected tissue.

It should be noted that free neutrons are probably unstable and if they escape capture, will undergo beta decay. The half-life of this reaction is estimated to be about one hour.

Protons

Protons are identical with the hydrogen nucleus. From a radiation standpoint in biology they are of greatest importance in that they are produced secondarily in tissue by impinging neutrons.

Because of the relatively high mass and charge, they are very potent ionizers. In accordance with the Bragg effect that we have already discussed, the ionizing power of the proton increases as the velocity decreases.

An example is: Penetration with protons is possible to a depth of 10 cm, if the propelling energy is about 115 mev. During the last cm of travel, ionization is six times that at the surface due to the lower velocity. In the last ½ cm the ionization is 16 times that at the surface.

The mass of the proton is slightly less than the mass of the neutron. This is in keeping with the fact that 1 mev of energy must be supplied to make possible the change of a proton to a neutron with the emission of a positron.

Ionizing Electromagnetic Radiations [19, 29]

Gamma Rays and X-Rays

Electromagnetic radiations involve a large range of wavelengths. Some waves have wavelengths hundreds of meters in length (longer than radio waves), while other waves have wavelengths of 10-12 cm. The term "electromagnetic" was applied when it was noted by Maxwell that electric and magnetic fields are always associated with each other. Changes in these fields produce wave disturbances.

The waves produced are rather complex and have an electric and magnetic component vibrating at right angles to each other, and both are perpendicular to the direction of propagation of the wave. This particular type of wave is found for all the waves of this group, no matter what the frequency.

Both gamma and x-rays belong to this general classification of electromagnetic waves.

Aside from frequency, there is no significant known difference between gamma and x-rays. Therefore, there is a range in which one finds "soft" gamma rays of the x-ray type or "hard" x-rays of the gamma ray type. In general, whatever is said of gamma rays also applies to x-rays.

Gamma rays originate in the excited nuclei of atoms. They represent the energy difference between the initial excited state and the lower energy state, which may or may not be the ground state of the atom. In other words, there may be several steps between the initial energy level and the ground state of the atom. In this case the original transaction may be followed by one or more additional gamma emissions in rapid succession. The nucleus is finally left in the stable ground state. The packet of gamma radiation emitted as a consequence of a single transition is termed a "photon."

The penetration of gamma rays is extremely great and, all other factors being equal, is inversely proportional to the density of the substance concerned. While alpha particles are absorbed in a fraction of a millimeter of aluminum and beta rays are absorbed by a few millimeters of aluminum, gamma rays can penetrate several cm of the same material.[19]

Since gamma rays have no charge, ionization in tissue is largely secondary. Some atoms, of course, have electrons knocked out of the orbitals by gamma rays and are thus ionized directly. However, these dislodged electrons usually have a relatively high energy and in turn produce ion pairs. This is where most of the radiation comes from for gamma radiation.

Primary Methods of Absorption of Electromagnetic Radiation[39]

Absorption of gamma rays occurs in three principle ways:

(1) The lower energy gamma photons are absorbed by what is called the "photoelectric effect." The photon gives up all of its energy to the orbital electron. Thirty to fifty electron volts of energy are usually required to dislodge the electron, the rest of the energy of the photon going into kinetic energy. This relation was first proposed by Einstein. The relation is:

$$h\nu = P + \tfrac{1}{2}mv^2$$

where h = Plank's constant,
ν = the frequency of radiation,
P = binding energy of the electron in the atoms,
m = mass,
v = velocity.

As stated previously, the energy of the gamma ray is usually fairly high and is much greater than the binding energy. Hence, the energy of the emitted electron is not much different from the energy of the incident photon. Obviously, the absorption due to the photoelectric effect is greater, the more tightly bound the electron. Hence, in a given element, a "K" electron may be several times more effective in stopping gamma radiation than is an "L" electron.

The Einstein relation simply states in mathematical terms a very sensible proposition. This is that the energy of the incident photon must equal the energy needed to dislodge the electron, plus the kinetic energy imparted to it.

(2) The second way a gamma ray may be absorbed is by the so-called "Compton recoil effect."

Consider an incident photon of wavelength λ, or frequency ν, with a velocity c. Consider that this photon is approaching an atom; and upon impact with an electron, the electron recoils with a velocity v at some angle ϕ.

Since to accomplish this, energy must be taken from the photon, the photon has in effect surrendered its identity and a new photon of lesser energy and frequency (ν') is ejected at an angle θ with the original photon.

(3) A third method of absorption of gamma rays involves very high energy photons of 1 mev or more. In this case, when a photon strikes matter (atoms), more particularly the heavier elements, some of them disappear as in the case of the photoelectric effect but by a different mechanism. Instead of knocking electrons from their orbits, some photons come in very close to the nucleus and disappear with the actual creation of ion pairs of opposite charge; this means with the production of electrons and positrons. In this case we have matter formed from the electromagnetic energy. The positron immediately disappears in the so-called annihilation reaction with the creation of two quanta of energy.

The annihilation reaction may be considered qualitatively as follows: when a positron is ejected, it enters into an atmosphere of negative

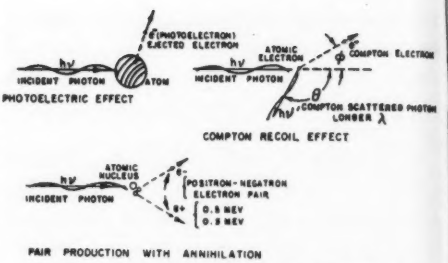


Fig 1. Methods of energy absorption.

charges (Dirac-Relativistic Quantum Theory, 1934). The obvious thing to happen is that the positive and negative charges will react, which they do. However, energy and momentum must be conserved. It follows, therefore, that an atom must participate in order to carry off the excess momentum to satisfy the requirements of conservation. Hence, pair production can occur only in the presence of matter, and the heavier the atom (larger), the greater the probability of gamma conversion in this way. If m is the mass of the electron and c the velocity of light, then for the creation of the positron and the electron, an energy of mc^2 is required for each.

In the case of the electron and positron $E = mc^2 = 0.511$ mev, or for both 1.022 mev. This then shows why only high energy photons are capable of this type of interaction.

To summarize the absorption of gamma radiation (also x-ray), we may now consider three qualitative pictures.

Minor Radiations

Just so that the terms will not be totally foreign, the particles or rays evolved by secondary radiations should be mentioned.

The emission of electrons following gamma ray impact have been discussed. The electrons thus produced by ionization have sufficient energy so that they themselves produce ionization. The subsidiary ionizing electrons constitute the so-called *"delta rays."*

When charged particles such as electrons near the end of their course in an absorbing medium, irregularities occur. During the final rapid deceleration or braking effect, the last bit of energy of the particle is converted into soft gamma rays.

These soft gamma rays are called Bremsstrahlung Radiation.[48]

Units of Radiation Intensity

Because of the diverse nature of different ionizing radiations (particle vs. wave), it is reasonable that different units of measurement of dose would be required. If one is considering particle radiation, the standard unit of intensity of radiation is the "curie." A curie is actually the radioactivity yielded by 1 g of radon in equilibrium with its parent substance radium and its disintegration products. The radiation of a defined curie is very complex, being made up of alpha and beta particles as well as gamma rays. While this complexity creates serious difficulties in usage and makes necessary many descriptive qualifications, it is nonetheless useful because it relates radioactivity to a given weight of radium. In practice the curie is most often defined in terms of disintegrations. In these terms a curie is the amount of radioactive material that will produce 3.7×10^{10} disintegrations/sec. A millicurie is then 1/1000 of this amount. A disintegration rate of 1,000,000/sec has been given a special designation of a "rutherford" (rd). There would then be 37 rd to a millicurie.[48]

If one is concerned with electromagnetic radiation, the standard unit is the "roentgen" or "r." This unit is based on the production by x-ray or gamma ray of 1 esu of charge in 1 cm^3 or 0.001293 g of air. This charge may also be considered as 83 ergs/g of air and is associated with the formation of 1.6×10^{12} ion pairs.[85] We shall see later that the use of the "r" unit in biological problems requires many qualifications, only some of which can be quantified.

Consideration has been made of the general ways in which x-rays and gamma rays may be absorbed in matter. If we are to consider the problem of effects of radiation on biological systems, it is necessary to consider more detail in the form of two additional problems. (1) How is the energy from radiation dissipated in a biological medium, and (2) what are the problems involved in actually determining the x-ray dosage or particle dosage to a given tissue? These two problems will be considered in order.

ENERGY DISSIPATION

General Consideration

It can be reasonably assumed that the magnitude of the biological effect of x- and gamma rays is some function of the amount of energy absorbed. It is, then, important that the biologist or engineer who studies the effect of radiation understand a number of factors and complexities in the absorption of energy by tissue.

In general when electromagnetic radiation strikes matter, it may (a) be transmitted through the material without change, or (b) be absorbed by one of the primary mechanisms we have discussed. However, if absorption by one of the primary mechanisms occurs, it is always possible for secondary effects to follow. An incident beam of x-rays may eject an electron from an atom by either the Compton effect or the photoelectric effect. This excited electron then becomes an ionizing force in its own right by virtue of its high energy, and its energy must be dissipated. Some energy is lost by the formation of ion pairs. This type of phenomenon may then go on to do biological damage. However, energy can be lost by other mechanisms that may or may not produce biological damage. One such method that is fairly important is that of fluorescent absorption.

Some general remarks should be made about the processes of fluorescence and phosphorescence[34] so that what follows in the discussion may be somewhat more clear. If a given amount of energy is transferred to a molecule, it may be absorbed by a process in which an orbital electron is elevated to a higher energy level but not released from the atom. In certain atoms or molecules this energy may then be dissipated by the excited electron's dropping back into a more stable orbit, releasing its energy in the form of light. Phosphorescence is generally considered as that case in which the electron remains in the excited state for only a short period of time before it drops to a more stable configuration with the emission of light. This is in contrast to fluorescence where the electron may remain excited for some period of time before the transition occurs. Such distinctions are of course

somewhat arbitrary within certain ranges of time. No effort will be made to adhere to this usual convention in the discussion of absorption of ionizing particles or electromagnetic radiation. Rather, all of the phenomena of this nature will be considered as fluorescent absorption. This fluorescent absorption is different from such effects as the Compton effect because the radiation that results from the fluorescence is a radiation characteristic of the emitting atom, and the wavelength is always constant for that atom. The characteristic radiation is always of longer wavelength, hence of lower energy, than the incident radiation. In this way energy from secondary radiation is lost, and no biological damage need be done.

It should be apparent that when ionizing radiation of any sort strikes a piece of tissue, the transformations of energy that occur can be a very complicated process. The incident beam is partly changed in direction and in wavelength and some of its energy is transferred to electrons which produce ionization of the irradiated object. Some scattered rays and some of the incident x-rays themselves undergo successive processes of scattering and fluorescent absorption and their energy becomes progressively dissipated. The electrons that are excited by the primary and secondary radiations also set up successive processes; the energy they possess may be transferred to still other electrons which in turn set up more secondary ionization.

The electrons that are excited possess much less ability to penetrate tissue than do the x-rays. However, some of them will escape out of the surface of the object. The rest will give up their energy to the object in the form of heat and chemical energy.

The first stages, therefore, in the sequence of events that leads from the irradiation of tissue to a biological event are the conversion of radiant energy into ionic energy and the conversion of ionic energy into heat and chemical energy in the tissue.[34]

To show the first stages of absorption of radiation of tissue, we consider the following diagram.

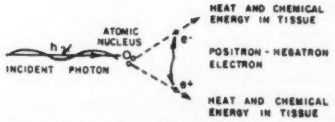


Fig 2. First stage of absorption of energy by tissue.

Quantitative Considerations of Energy Absorption

Determination of Dosage

The biological effect of radiation can be assumed to be proportional to the absorbed energy. Since the absorption of energy is a very complicated process, it is necessary to find some method of measuring the amount of energy actually absorbed by the tissue during irradiation.

The direct measurement of energy absorption in tissue is practically impossible. Indirect methods utilizing the "r" unit are essentially measures of the quantity of radiation that is absorbed in air, and the dose in tissue is then calculated from this value.

The absorption of x-rays or gamma rays is dependent upon the nature of the elements of the absorbing body.[101] The elements of air have very much the same atomic weights as the elements that make up tissue, and hence one would suspect that to a first approximation, at least, there must be some kind of parallelism between the way x-ray is absorbed in air and the way it is absorbed in tissue.

This expectation can be demonstrated under certain very restrictive conditions. For example, if the amount of tissue to be irradiated is very small, say like an insect egg, and is suspended in air so that the scattering radiation reaching it is at a minimum, the amount of energy absorbed in the tissue is directly proportional to the intensity of the beam as measured in r/sec by means of an open ionization chamber. The dose of x-ray administered in such a case is expressed in r units simply by multiplying the duration of the exposure by the intensity of the beam in r/sec. In air or in small amounts of tissue both scattering and fluorescent absorption are negligible, and there is no attentuation of the x-ray beam because of these causes.

This method of calculating doses becomes very

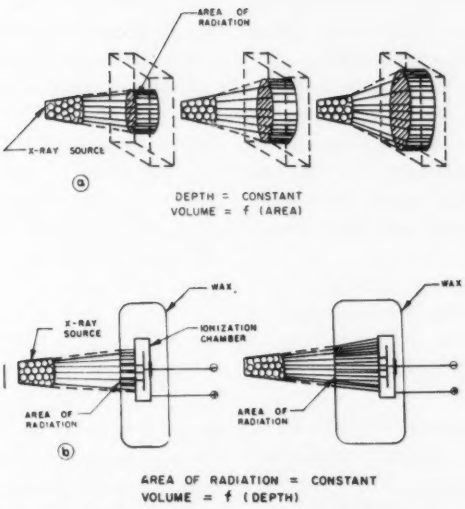


Fig 3. Two methods for measuring x-ray absorption.
a. Variation of field of radiation to give different volumes.
b. Variation of depth penetration to give different volumes.

inaccurate when a large piece of tissue is irradiated because it fails to take into account the effect of fluorescent absorption and scattering. How important these latter factors are depends upon the mass or volume of the tissue irradiated. The error involved may, in some cases, be quite large.[101]

Fluorescent absorption must be considered in determining the distribution of absorption of energy in different parts of the tissue. If the wavelength of the incident beam is long, say 2A, the energy is absorbed in the superficial layers. If the incident beam has a short wavelength, say 0.1A,[32] then it penetrates more deeply, and while the amount of fluorescent absorption is small, what there is tends to be uniformly distributed at different depths in the tissue.

With short wavelength radiation, scattering becomes of primary importance. If one uses a 0.1A wavelength and irradiates muscle, the intensity of the beam is reduced by half after passing through 5.0 cm of the tissue.[73,101] This means that since scattering has occurred in all directions, one must not only measure the absorption from the primary radiation, but also the radiation from all the scattered beams in order to arrive at a dose at the tissue level.

From this we should conclude that as far as larger amounts of tissue are concerned, there are two variables in estimating dose: (1) the volume or amount of tissue, and (2) the wavelength of the incident beam.

Some Problems of Dosimetry

Since the dissipation of energy in tissue can be very complicated, it is necessary for quantitative work to be able to estimate the true energy absorption by some indirect means. While it is general practice among modern biologists to simply quote the "r" dose in air independent of the volume of tissue irradiated or the wavelength used, it should be obvious from what has already been said that this method would give no true idea of the quantity of energy absorbed. In other words, such a practice means that one can never do more than interpret qualitative effects of irradiation if such practice is followed. One can never quantitatively compare results between species; in fact, even results for different sizes of animals of a single species

would be uncertain.[73] For any quantitative work, of course, it is necessary to be able to say exactly how much energy is absorbed and where.

If such is the case, why is the practice of simply quoting air values followed? The answer is that it is very difficult ever to achieve a true description of the distribution of absorbed energy. One may account for many factors, but one never knows if one has accounted for all of them.

To give some idea of the magnitude of possible error in simply quoting "r" values from air, one can consider work that has been done on model systems. Two such systems are shown diagrammatically.

If one uses a block of wax of the proper kind, one finds that x-rays are absorbed by the wax "phantom" in about the same manner as they are absorbed by soft tissue or by water.

Using a wax phantom it is possible to irradiate a defined surface area and measure the intensity of the x-ray beam with and without the presence of the wax phantom.[72] One may also imbed an ionization chamber in the wax phantom so that different volumes of wax appear between the chamber and the x-ray source.[72,79] Then, as may be seen from the diagram, the volume of the phantom that is irradiated may be varied by simply increasing or decreasing the diameter of the "field of irradiation." When such an experiment is done using a constant x-ray wavelength it is found that there may be as much as a 70 per cent increase in x-ray intensity in the presence of the wax surface.[72] When a similar experiment is done in which skin is irradiated instead of a wax phantom, errors due to backscattering may be as much as 50 per cent.[38]

If one holds the field of irradiation at a constant value and varies the depth of the ionization chamber in the wax model or phantom, errors in calculated dosage may be as great as 50 per cent.[79]

Studies of model systems have also included experiments in which the quality of radiation has been investigated as a variable in measurement of radiation dosage. If one considers absorption of radiation at the surface of a film of water or at the surface of skin, absorption may vary over a two-fold range and the variation follows an irregular course.

The conclusions of such experiments are important to both the biologist and the engineer because the absorption of x-ray in the skin may very well follow a similar course to the absorption in a surface film of water. Therefore, in the conditions of many biological experiments it is impossible to calculate in a simple way the amount of energy absorbed by tissue from an x-ray beam when the intensity of the beam is expressed in "r" units as measured in air.

From this discussion it should be clear that for certain limited conditions the amount of energy absorbed by the tissue is directly proportional to the dose of x-ray expressed in "r" units measured in air. However, these conditions are very limited; and the relationship does not hold if (1) the size or shape of the irradiated object varies, or (2) if the wavelength of the incident beam varies.

Method for Correction of Dosimetry Errors

In biological experiments it is very likely that objects of different size and/or different volumes of tissue will be irradiated, and it certainly is likely that different wavelengths will be used, especially under field conditions.

Therefore, it becomes necessary to devise methods of measurement which either avoid such variables as have been discussed, or when the variables occur, take them into account. Certainly as a minimum, one should be aware of the possible errors so they can be considered in interpreting any results.

In partial summary there are a number of ways one can either avoid or evaluate the errors that have been discussed:

(1) Very small pieces of tissue, such as insect eggs, can be suspended in air and irradiated. If no scattering occurs from surrounding objects, then the amount of effective scattered rays will be negligible because the egg is very small. The small size of the egg allows the x-ray beam to pass through it with a minimum amount of attenuation, and therefore the energy is almost

uniformly absorbed throughout the egg. Then r/sec × time is equal to the dose. Of course, one may not always want to work with such items as insect eggs. Therefore, another method of control must be used.

(2) In any one series of experiments the doses used may simply be compared if the wavelength is constant and the size and surroundings of the object of irradiation are constant. This is the system most usually followed. In this case, again r/sec in air × time gives a dose. It must always be remembered, however, that this dose is relative and is valid only for the particular series of experiments in the conditions that have been specified and certainly in no way represents an "absolute dose in r." This method is all right for obtaining comparable measurements, but it should be apparent that it can never lead to anything except a qualitative interpretation of results.

(3) For those more concerned with quantitative measurements it is possible to construct special small ionization chambers that can be embedded in wax or water models of the tissue to be irradiated. The intensity of the x-ray that reaches this special chamber is then measured in r/sec. One then uses exactly the same beam to irradiate the biological tissue, and the dose to the tissue that corresponds to the site of the small ionization chamber in the model may then be expressed in "r." This technique is possible because living tissue absorbs x-rays in much the same way as does water or wax. This obviously is a very tedious procedure to follow and it probably accounts for the lack of popularity of the method. Also it must be remembered that animals are most certainly not homogeneous in their makeup. This introduces an additional variable that must be considered at all times. For example, with short wavelength x-rays of the range of 0.05A, absorption occurs almost equally in bone, muscle, and water. However, for longer wavelengths of 0.3A, the absorption of bone is twice that of muscle and water. Therefore, even if models are made and used for estimation of dose, the doses are nothing more than approximations to the absolute "r" dose delivered to the tissue.

The difficulties encountered in measuring x-ray dosage have been sufficiently indicted by now. The possible errors discussed may easily lead to errors of 100 per cent if one does not even consider such problems as change of wavelength. It is impossible to assess the reliability of measurement of dose estimates by many authors, and attention must always be paid to this phase of any publication. However, in any one series of experiments carried out under constant conditions, the doses may be inaccurate on an absolute basis, but at least the results will be comparable with each other.

When a different series of experiments is considered, any comparison must be made with caution.

Units of Interest

Several attempts have been made to overcome the complications encountered with using the "r" unit in systems different than air by simply changing units. Hence one may use an REP unit that is actually a "roentgen equivalent physical" unit. This unit is defined as the amount of ionizing radiation that is capable of releasing the same energy in tissue as one r of x-rays or gamma rays. As will be recalled, this amount of energy is approximately 83 ergs/g of tissue.

Since ultimately one is more interested in the amount of energy absorbed by a system than the amount of energy released by the radiation, a unit that describes this absorption is more useful. Such a unit is the "radiation absorbed dose" or the RAD. One RAD is defined as the amount of irradiation that results in the absorption of 100 ergs/g of tissue.[42] The definition of the RAD does not specify the medium in which the energy is to be absorbed. Therefore, to overcome this shortcoming it is necessary to state the medium that is to be considered.

Different types of radiation (particles vs. electromagnetic) may be absorbed in different ways in tissue. Nevertheless it is desirable to be able to compare one form of radiation to another. To do this a symbol RBE (relative biological effi-

ciency) has been defined. RBE is used to compare the effectiveness of the absorbed irradiation delivered from different sources or in different ways. It signifies that a particular amount of irradiation can be compared to a second amount of a different radiation by comparing the two biological responses. In this way one may state that the RBE of slow neutrons relative to γ-radiation is 5. This means that one RAD of slow neutrons produces a particular biological response to the same degree as does 5 RAD of γ-radiation.

The concept of RBE represents a gross oversimplification in that the degree of effectiveness of radiation in a living system may be modified by many physical and biological factors. Thus no simple comparison is completely valid. Despite this, the concept of RBE is convenient and continues in use.

For application to man it has been convenient to develop a unit directly applicable to the human organism. Such a unit is a REM or "roentgen equivalent man" unit. A REM is the amount of ionizing radiation which, when absorbed, will have the same biologic effect as one "r" of x-rays or gamma rays. Up to 1956 a REM was generally defined as REM = REP × RBE (relative biological effectiveness). It has been suggested by the International Commission on Radiological Protection[62] that after 1956 the following definition be used: REM = RAD × RBE. Of course, the REM unit has the same objectives and limitations as does the RAD and RBE. It is nonetheless useful in discussing radiation protection or radiation exposure.

The evolution of the RAD and REM units and the RBE can be shown conveniently in tabular form (Tables I and II).

TABLE I

Evolution of the RAD and the REM[62]

To the present	After 1943 (REP)	After 1953 (RAD)
Roentgen (r) applied only to measured dose of x- or gamma-rays	Applied to measure absorbed dose in soft tissue. Apply to any type of radiation	Applied to measure absorbed dose in any medium. Applied to any type of ionizing radiation
1 esu/0.001293 g air	83-93 ergs/g	100 ergs/g
	REM	REM
	Use only for exposure records	Use only for exposure records
	REM = (RBE) × REP	REM = RBE × RAD

TABLE II

Evolution of Relative Biological Effectiveness (RBE)

1943 to 1953		1953 to 1956	
RBE when applied to	has a value of	RBE when applied to	has a value of
x-rays and gamma-rays	1	x-rays and gamma-rays	1
electrons± and beta particles±	1	electrons± and beta particles±	1
slow (thermal) neutrons	5	slow (thermal) neutrons	2.5
fast neutrons	10	fast neutrons	1 to 8
alpha particles	20	alpha particles	10
		protons	10

1956 RBE as a function of linear energy transfer (LET)

RBE when applied to	has a value of	RBE when applied to	has a value of
200 kv x-rays	1	neutrons of the energies shown below	
0.1 mev beta particles	1.08	thermal (mev)	2.8
1.0 mev beta particles	1.00	0.0001	2.2
0.1 mev protons	10	0.005	2.4
1.0 mev protons	8.5	0.02	5
5 mev alpha particles	15	0.5	10.2
1 mev alpha particles	20	1.0	10.5
		10.0	6.4

In future RBE may be a function of the linear energy transfer (LET) for each specific type of damage.

Actually the REP, the RAD, and the REM are convenient descriptive units for the purpose of conversation, keeping records or setting safety standards. The fault in common with each unit is that it effectively avoids the basic problem of describing the actual *amount* of energy involved, and hence it can only be defined qualitatively by experimentation. As a result none of the units can be used for specifying radiation. They do serve their purpose well, however, as a constant reminder that dosage specification in a biological system is a complicated problem.

(Adapted from reference 62)

RADIATION OF LIVING SYSTEMS

General Considerations

X-rays and gamma rays in general have two types of biological action that can be easily and accurately measured. These are (1) production of injuries in living cells and (2) production of genetic mutation in cells.

Before discussing such problems as lethality, it is necessary to presuppose that it is known what a cell does when it is alive, and therefore it will be necessary to review briefly the process of reproduction of a cell. This process generally implies, if it does not prove, that the cell is alive.

When any cell divides, it goes through a continuous series of changes in which one cell ultimately becomes two cells. For the sake of convenience there have been described a series of "stages" in this division process. Actually since the process is a continuous process the stages represent nothing more than an arbitrary selection of certain forms one may see in the sequence of cell division. Nonetheless these stages are valuable in the transmission of information. When a cell is not actually in the division process, it is said to be resting or in a "resting stage." When the process of cell division begins, the cell moves out of this resting stage and the mitotic (i.e. cell division) activity begins.

Process of Cell Division (Mitosis)

Most of the process of cell division is centered about the action that occurs in the nucleus of the cell. It would appear that all parts of the cell except the nucleus, namely that part called the cytoplasm, simply "go along" with the division until the late stages when the cytoplasm then divides. For this reason our discussion here will be confined to the action of the nuclear material of the cell during the division process.

Following the resting stage of the cell the nuclear material (namely chromatin), which has been scattered throughout the nucleus, begins to form thread-like structures. These thread-like structures align themselves along a plane at the center of the nucleus and form the chromosomes of the cell. The chromosomes are the structures

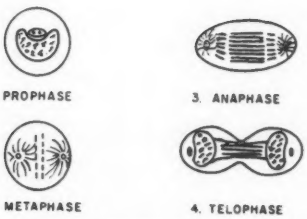


Fig 4. Process of mitosis.

that carry the "genes" or the hereditary units of the animal. It is the formation and alignment of the chromosomes that is referred to as the prophase of cell division. While this orientation of nuclear material has been occurring, a small extranuclear body called the centriole has divided into two parts, and each part has moved to opposite sides of the nucleus. These centrioles now act as loci directing the activity of the nuclear rearrangements.

Once the chromosomes have lined up in an equatorial plane arrangement, they split longitudinally and each half begins its movement toward the controlling loci, the centrioles. The division of the chromosomes is referred to as the metaphase of cell division. The movement of the divided sections of chromosomes away from the equatorial plane is called the anaphase of cell division.

When the chromosomes have moved into their respective halves of the nucleus, the nucleus and the cytoplasm begin to divide into two parts. This division process is called the telophase stage. When the division is complete there are then two "daughter cells" each exactly like the original parent cell. The characteristic feature of this division process is that the nuclear material is divided exactly into two parts, each half going to a new cell and each cell containing the same number of chromosomes as the original parent cell. This entire process is called mitosis. Graphic representation sometimes assists in visualization of this process.

All cells from all sources are capable of undergoing mitosis. Different kinds of cells have different mitotic rates however. If one has a large number of cells all of the same kind, they do not all divide at once but rather only a small part of the population is actually dividing while the remainder are in the resting stage. One can determine the percentage of cells that are dividing simply by cutting a thin slice of tissue, staining it so that the nuclear material can be seen and counting the number of cells that are in some stage of cell division other than the resting stage. Any cell not in the resting stage is referred to as a "mitotic figure", and by knowing the number of mitotic figures and the total number of cells in the sample one can express the rate of division as a "mitotic index." In this way, then, one can obtain some idea of the number of dividing cells in a culture by simply counting the number of mitotic figures, and if one wishes a quantitative expression, one may use the mitotic index.

Reduction Division of Germ Cells (Meiosis)

In certain cells, namely germ cells, or those cells that are involved in sexual (as compared to asexual) reproduction, the cell can undergo a process whereby the number of chromosomes is reduced to one half during the cell division

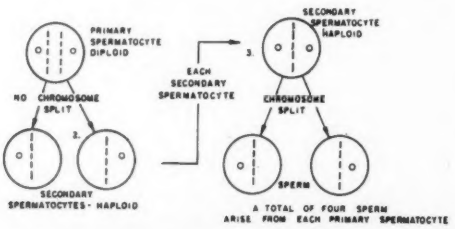


Fig 5. Process of meiosis.

process. This process is referred to as "reduction division" and the entire process through which the cell goes is referred to as "meiosis." To compare this process with mitosis, a diagram of meiosis is helpful.

If changes are produced in the chromosomes of these germ cells by means of irradiation, the efforts can be passed on to the next generation of offspring and the genetic effects are said to be "mutations."

Radiation Injuries

The injuries produced by electromagnetic rays are graded and range from lethal to completely reversible injuries.

Mortality

All living tissue is killed if large enough doses of x-rays or gamma rays are administered. Actually, the percentage mortality of an irradiated group is very often used as a measure of the biological action.

If one is going to use this criterion of biological action (namely mortality) and state the percentage of cells or organisms that die, it is necessary to define the criterion of death and to state whether it occurred immediately or was delayed.

An example of this is as follows: If x-rays are administered to certain types of eggs before cleavage has occurred (these experiments were actually done using the eggs of the frog[70]), the egg can absorb 72,000 r and still divide. However, if 400 r is given at the same stage, death will occur before the gastrula is formed.

In stating the lethal dose for any tissue, then, it is necessary to define the type of lethal action and to say if it is immediate or delayed. If the cells die some time after the irradiation, the duration of the latent period as well as the condition of the tissue during the latent period must also be clearly defined.

Inhibition

Injury to cells that is less severe than lethal can also be measured. X-rays and gamma-rays can simply inhibit the growth in plants. For such a study it would be required that irradiated roots and nonirradiated roots of a similar kind be grown together. The inhibition of growth due to irradiation can then be estimated. This same technique is applicable to growth of tissue cultures or other systems where a suitable criterion of damage can be realized.

Injury produced by x-rays can also be measured by the extent of the percentage inhibition of mitosis (cell division) in one experimental system. In such measurements the number of mitotic figures in irradiated preparations is compared with the number in unirradiated cultures of the same kind.

Genetic Injury

In measurements of the genetic action of x-rays or gamma-rays, *Drosophila* (fruit flies), corn, *Tradescantia* (a plant called "Wandering Jew"), or mice are generally used. In a typical experiment with flies, an adult male is irradiated and allowed to mate. The offspring of this mating, the F_1 generation, are then mated and the F_2 generation is produced. The percentage of F_2 flies that show mutations, corrected for normal mutation rate, is then the measure of action of the radiation.

There have been many other methods used to evaluate the nonlethal effects of irradiation. The above examples are given only to show a few methods. Other methods will be discussed in detail in a later section.

Simple Dose-Effect Relations

The relation between energy absorption and the magnitude of biological effect has been the object of a great deal of study.[7] There are many biological effects of irradiation that follow a simple dose effect relationship. For example, radiation induces a delay in cell division of certain tissues in the eye. This delay in cell division varies in proportion to the radiation dose from 50 to 4000 r.[33] Observations of this type and also the simple effect of time delays in the development of an injury or other end-points have not been successfully interpreted to date. It is the effort to complete the interpretation of such observations that occupies the time of many radiobiologists today.

If one has a macroscopic (easily observed) event that may be used as an indicator of radiation damage, one may then study radiation damage in the simple way of just determining the frequency distribution of the macroscopic effect in a given irradiated population.

Exponential Dose Response

In the simplest possible case each unit amount of radiation absorbed will produce equal damage. Each separate amount of radiation seems to act independently and therefore the effects are additive. There is therefore an "equal dose equal response" relationship.

In the more complicated case it may be that as successive equal doses of radiation are given the damage done is greater than would be expected. One must then conclude that the effects are compounded and each additional dose of radiation adds to some latent effect of an earlier exposure. Should this "equal dose unequal response" be the case, it is necessary to obtain additional information by studying the effects of divided doses if one wishes to obtain an interpretation.

Now, if the damage follows the simple rule of an "equal effect for an equal dose," one is led to the following result. Suppose that a certain amount of radiation produces the event under consideration in 10 per cent of the population. Then an additional equal dose would produce the event in another 10 per cent of the remaining population (90 per cent). A third additional dose would produce the effect in 10 per cent of the remaining 81 per cent which remained unaffected after the second dose and so on.

This situation produces a Poisson distribution. As a matter of fact, this is exactly the type of distribution for any sequence of events where each action is independent of all other actions of the same kind that are going on in a fixed population.

If we indicate the number of organisms exposed to irradiation as N_0 and the number of organisms which remain normal after exposure to a dose D of radiation as $N(D)$, then we can say that the frequency of the failure to respond to irradiation varies as a function of the dose according to the law

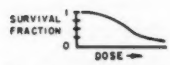


Fig 6. Dose response relationship.

$$\frac{N(D)}{N_0} = e^{-\lambda D}$$

or this may be written as

$$\ln N(D) = (\ln N_0) - \lambda D$$

If one now plots this information as shown, then lamda (λ) is the "rate of action" of the radiation and is equal to the slope of the line on the semi-log plot.[33]

If the occurrence of some event attributable to radiation behaves in the manner shown, we say it follows an exponential dose-action or dose-response curve.

Under certain conditions a number of similar events may occur in the same organism. For example, numerous chromosome breaks may appear in one cell. The fraction of cells which remain normal and show no chromosome breaks will follow an exponential dose response curve. It follows logically that the occurrence of cells that show 1, 2, 3 or more breaks should relate to the occurrence of breaks in the same way; that is, it should follow a Poisson distribution. This result is seen to be true in certain genetic experiments, and after long times of radiation the total frequency of breaks per cell may become larger than 1. In fact the number of breaks per cell will be directly related to the total dose of radiation expressed as $f(d) = \lambda D$.[33]

The lambda in this equation is the same as that seen in the previous equation and is a coefficient that can be called the "rate of action." This coefficient is in reality a probability and is introduced purely as an empirical constant. A more substantial understanding of the significance of lambda requires an understanding of the mechanism of action of radiation.

If one can define the parameters that control the "rate of action," one should then be able to

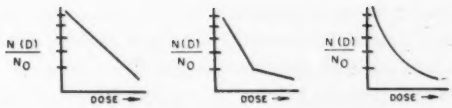


Fig 7. Types of dose response curves.

decide what factors are important in the effect of radiation on a biological system. In what follows, an attempt will be made to see what is known about how λ can be defined.

To understand the simple exponential dose-response curve, it is necessary to determine if the exponential form follows for only a limited range or if it holds over a very wide range down to very low doses. Some experimental curves of the survival of unicellular organisms follow an exponential form down to a small fraction of survival. This indicates that there must be a very significant homogeneity of population with respect to radiation resistance. In other cases the semi-log plot flattens at a low level, thus indicating that a small proportion of the initial cell population displays some special resistance to irradiation.

If it is found that the probability, λ, of a given biological event has different values for different groups throughout the population, then the simple exponential curve would have a definite upward curvature and would not be a simple straight line, nor would it be as simple as the two-step curve. These three effects are shown diagrammatically in the accompanying figures.

Theoretical Considerations

The significance of the exponential dose-response curve depends upon whether the response occurs at very small doses. The reason for this is as follows: The concept of a fixed probability for radiation action implies that there is a finite chance of detecting the occurrence of an event due to the radiation, no matter how large the population examined or how low the dose of irradiation. In other words, each bit of radiation even down to a single particle or photon must be capable of producing an observable effect.

The use of lethal action as a measure to test the above hypothesis is not very satisfactory. Very small lethal effects of radiation cannot be measured accurately under normal circumstances, since it is necessary to count the number not killed rather than the number that are killed. In other words, one must score the nonoccurrence rather than the occurrence of an event and this becomes complicated.

On the other hand, genetic effects can be measured accurately even at exceedingly low frequencies such as 1 in 100,000 for fruit flies or 1 in 10,000,000 for bacteria,[33] because the frequency of positive effects is scored directly. For many classes of mutations or changes in chromosomal make-up investigated in this way the dose-effect curve follows the exponential form down to very low doses.[90]

Effective Volumes and Effective Areas[33]

So far "rate of action," λ, has been considered as the probability of producing a certain observable event of some kind in an organism for each unit dose of radiation. Under this circumstance the "dose" of radiation should indicate in general the actual amount of energy dissipated per unit volume of material. While this view of radiation dose is useful, it should be remembered that it is only one of the ways that energy dissipation may be viewed.

Energy dissipation as we have discussed it applies to all types of radiation. It is not related to the kind of radiation that one considers, nor is there a need to relate energy dissipation to the exact mechanism of the physical action of the radiation in biological systems. For this reason, one can relate the number of biological events caused by radiation to the number of primitive elements of radiation (particles or photons, activations or ionizations).

Consider again the equation for an exponential dose-response curve: $N(D)/N_0 = e^{-\lambda D}$ The exponential term — λD must be dimension-

less. For this to be true the constant λ must have units which are the reciprocal of those used for the dose. By defining the dose of radiation in different ways, one may then obtain different meanings for the rate of action, λ.

For example, if one refers to a dose of monochromatic x-ray in terms of the number of photons of energy absorbed, the rate of action then represents the probability of the occurrence of the biological effect observed per photon of energy absorbed. If the photon is now considered to be absorbed in some unit volume of material, λ then represents the probability of occurrence of the biological event per photon of energy absorbed per unit volume of material.

To see how such a concept works in practice consider the following example.

It has been shown that the probability of bacterial "killing" by ultraviolet light equals 10^{-20} for every photon absorbed in $1cm^3$ of bacterial matter. Since the photons are absorbed at random, the death of a particular bacterium has the same probability as the absorption of one photon within a volume of 10^{-20} cm^3 of bacterial matter.[33]

This volume is called the "effective volume" for killing the specific bacterium under the set of specified conditions.

In this way the rate of action is expressed as an "effective volume" for the production of the biological "event" under consideration for the "average activation." The ringer in this whole system, of course, is that which has already been discussed; namely, the estimation of the average energy of the activations that occur in tissue.

If one now chooses to represent the dose of radiation in terms of the charge flux within the material instead of energy absorbed per unit volume, the rate of action represents a different probability. It is possible to determine the number of particles or charge that cross a unit area within the material under consideration. By knowing this flux and the number of biological events that result from the energy absorption, one can calculate the size of an area which is crossed by a particle with a probability equal to the probability of occurrence of the biological event under consideration. An example of this is the frequency of "death" of bacterium coli caused by polonium alpha particles. It has been observed in an experiment where bacteria were irradiated with polonium that there is one death per 2×10^8 particles/cm^2. Therefore, the chance of a killing effect equals the chance of crossing an area $\frac{1}{2} \times 10^{-8} = 5 \times 10^{-9}$ cm^2 laid in front of an alpha particle beam. An area of this size is called the "effective area" or the "effective cross section" for the specific killing effect of the specific form of energy used.[33]

THEORIES OF ACTION OF RADIATION[7,11,33,53,74]

Target Theory

So far the factors discussed do not require that any particular theory of action be assumed to describe the phenomena of radiation effects. Actually all that has been done is to describe physical parameters that have been observed or measured in conjunction with the action of radiation.

To understand and to be able to generalize about the action of radiation it is necessary to formalize our knowledge into new situations. Two principle efforts in this direction have been made and the efforts have been formalized by the names "Target Theory of Action of Radiation" and "Indirect Theory of Radiation."

The relation between these two operational concepts may be thought of in terms of a model. Assume that we have a sphere of unknown make-up suspended in a water medium. We can observe that when energy is applied to the system the sphere is broken. Now the sphere could have been broken by at least two mechanisms. The energy could have passed through the walls of the containing vessel, then through the water and have interacted directly with the sphere in a fashion that could fracture the sphere (target theory). However, it is also possible that the energy could have interacted with the walls of the container, have set up pressure waves in the fluid and have fractured the sphere by production of a secondary force (indirect theory).

Admittedly the model is artificial and oversimplified and if the problem is only to break the unknown sphere, it makes little difference which is the correct mechanism. If, however, it is our purpose to learn something of the characteristics of the sphere and something of the nature of the energy used, then a detailed knowledge of the mechanism of breaking the sphere is essential to our understanding.

The same problem exists in radiobiology. An attempt to understand how radiation works in a biological system makes it necessary to understand the evidence that leads to the "target theory" and the "indirect action theory" of action. Also it is necessary to have some feeling for the consequences of acceptance of any theory.

In what follows an attempt will be made to discuss the basis and the implications of both the target theory of action and the indirect theory of action of radiation. When the indirect action theory is discussed, it will prove necessary to discuss in some detail the action of radiation on water and inorganic substances. This discussion should serve at least two purposes: (1) because all biological systems contain both large amounts of water and some inorganic substances, action of radiation on both of these systems must always be kept in mind; and perhaps more importantly, (2) it should illustrate that radiation has certain actions that are the same no matter what the medium of study is. To say this in another way, all knowledge of action of radiation, no matter what the source, must be reviewed and kept constantly in mind for the interpretation of the biological action of radiation. While each individual fact may not be interpretable in terms of a biological system, the background of information must always be available.

One factor that has been coming progressively more clear in modern biology is that observable macroscopic biological phenomena are directed primarily by submicroscopic structures found within the animal. Examples of this are seen in the action of genes, in the action of vitamins and in the action of hormones. In each case there is a gross macroscopic event controlled by submicroscopic structure or substance. Because of this it seems reasonable that the chance of an eventual observable event to occur is particularly high whenever an activation or an ionization occurs within or very near to the key elements of an organism. To put this another way, it would seem reasonable to assume that a charged particle that crosses the nucleus is much more likely to produce a genetic effect than a particle which crosses the cytoplasm only and misses the nucleus.

In the formulation of the target theory one must assume that a definite biological effect, such as a gene mutation or even death of a cell, results whenever an ionization occurs within some well-defined submicroscopic structure such as a gene. According to the target theory, the structure itself constitutes a "sensitive volume" whose size coincides with the "effective volume" for production of the effect by an ionization.

Calculations have been made which point out that an ionization within a group of about 1000 atoms may produce a specific mutation in a fruit fly sperm from eosin to white eye color in the adult animal.[95] It is from such estimates as that that the opportunity arises for determining the size of the key microscopic structures from radiobiological investigation.

There have been many extensive studies of the dose-effect curves under a variety of conditions. Many of these results have been generally consistent with the theory. The main difficulty with this work has been that the experiments have not been crucial in nature and lend only passive support to any theory.[53]

In the meantime, much of the indirect evidence that has accumulated is unfavorable to the target theory. If the randomness of biological effects depends primarily on the random location of the primary actions, the correlation between these random events should be fixed primarily by the geometry of the key structures of the organism. In other words, the slope of the dose-effect curve should be independent of environmental factors such as temperature or the biochemical condition of the organisms. We shall see later that this is not always the case.

It should be pointed out that the demonstrated

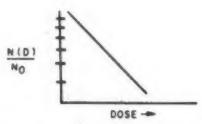


Fig 8. Sigmoid survival curve.

influence of any one environmental factor may be interpreted from the standpoint of the target theory by simply adapting the working model. However, the repeated accumulation of evidence that requires a special interpretation, certainly detracts from the attractiveness of the working hypothesis of the target theory.

Sigmoid Dose-Effect Curves

Most of the dose-effect curves that have been obtained are sigmoid in shape. The initial flat portion of the curve indicates that no observable biological effect is detected until a certain amount of radiation has accumulated.

One would think it should be possible by detailed analysis of this curve to provide information on the accumulation of radiation in a system prior to the occurrence of a biological effect. In practice, however, such analysis has not yet been possible.

From the standpoint of the target theory, an effect which follows a sigmoid curve can be visualized as resulting from a definite number of latent "single hit" effects that must occur and must be prerequisite to the appearance of the biological indicator used to assess radiation damage. For example, if one uses recombination of chromosomes as an indicator of radiation damage, it is observed that the recombination follows a sigmoid curve. However, before recombination can occur, the chromosomes must first be broken. These single breaks in the chromosomes, required before recombination can occur, follow an exponential curve.[87]

In cases where there is no direct evidence regarding the nature of the prerequisite "single hit" effects that are required to precede a biological action, the model suggested by the target theory represents only uncertain speculation.

Time-Intensity Studies

So far we have considered the dose of radiation in a given experiment as though it were all supplied at a single time. We have not considered the possible influence of the rate of administration upon the eventual effect we choose to observe.

Actually, equal doses can be delivered in very short and intense packets or over long periods of time at a very low intensity. As an example, one can deliver a dose of 10r of x-rays in less than one microsecond. 10r corresponds to approximately 1000 ergs/g in tissue and has been shown to have a definite biological effect under certain conditions. This same dose can be delivered at a steady rate by a weak gamma ray emitter over a period of weeks, months or even years.[33]

If one can control the distribution of radiation over the course of the experiment, it presents in principle an opportunity for investigating the mechanism of radiation effects. Such studies are referred to as studies of the "time-intensity factor" or simply as the "time factor."

There are two general approaches that have been used for the study of this time factor. (1) The most commonly followed practice is to keep the intensity of irradiation constant throughout each experiment and then to vary the exposure in a series of experiments in inverse proportion to the duration of the treatment. (2) A second method is that each treatment may be fractionated into two or possibly more, short, high intensity doses and the interval between the doses varied in a series of experiments.

If the separate photons or packets of energy from the radiation contribute independently to the observable effect as would be required by the target theory, one should of course not expect to find an influence of the time factor. In terms of the exponential dose-effect curves, the implication is that if the curve is truly exponential, then the effects of irradiation are independent of the rate of delivery of the irradiation and hence independent of time. In many examples this is exactly the effect that is observed. One must of course know that the physiological prop-

erties of the treated organism remain constant during the period of time the radiation effects are studied. For example, the sperm cells of a fruit fly remain in a constant condition for periods up to about one month. During such a period, equal doses of irradiation variously distributed during this period produce equal genetic effects.[64] If, however, equal doses are continued for a period over one month, the sperm cells may die from causes totally unrelated to the radiation.

If one considers a dose-effect response that follows a sigmoid shape instead of an exponential shape, the time factor may very well be of importance. In a few cases that have been investigated, the relationship between the time factor and the mechanism of origin of the biological effects seems fairly clear. One example of this is the case where two separate breaks in the chromosome appears.[87] Here it seems plausible that the two breaks may not combine to yield the final rearrangement if they arise at two distant instants of time. That is to say, two separate breaks may not recombine if they occur more than a few minutes apart. In this way, a given dose may become less effective if it is spread over a long period of time.

Indirect Theory of Action of Radiation

If we are concerned with the investigation of a method of action of radiation on biological systems, it is necessary to remember that biological systems are approximately 90 percent water. Hence one is led immediately to a consideration of irradiation of water or aqueous systems and from this to the postulation that radiation may affect biological systems through its action on water.

Two possibilities then arise:

(1) A molecular ion may be formed because sufficient energy has been absorbed by the molecule to displace an electron, or

(2) The molecule may be left with a higher level of electronic energy but still unionized.

Ions and Free Radicals

In general, one may say that practically all the energy given up by the charged particle must appear as either energy of ionization or excitation. The amount of energy to produce ionization is called the "ionization potential" and has been measured for many compounds. If one considers ionization in a gas, it would appear that the amount of energy given up per ion formed in the gas is usually about twice as great as the ionization potential.[2] This means that about half of the energy given up must go into excitation, and hence ionization and excitation are generally of about equal importance in a gas.[34] The excited states discussed here are the same as those we have disscused under fluorescent absorption. The molecules formed will undergo all the reactions one normally studies for excited molecules in photochemistry. Photochemical reactions in general occur because the energy of the molecule in an excited state is usually greater than is the energy of the chemical bonds in the molecule. Therefore, by proper rearrangements of the electrons, the molecule may disassociate or break into fragments. These excited-molecule reactions will always occur when high energy radiation passes through matter.

Ions may also give rise to chemical effects such as those we have just discussed. These chemical effects may arise from (1) dissociations of ions, (2) reactions of ions with other molecules, and (3) the dissociation of molecules upon neutralization of positive and negative ions when conditions are right for the total ionization potential energy to be made available for bond breakage. Molecular dissociation may then be produced both by ionization and by excitation.

If one considers molecular dissociation for large organic molecules, the dissociation may result in the formation of stable product molecules. For example, one may irradiate acetic acid, then $CH_3COOH = CH_4 + CO_2$. For small molecules, however, small stable forms into which the molecules can disintegrate do not exist. Therefore, such molecules as water will give rise to H^+, OH^- or H^+, H^+, O^-. Hence with small molecules the first result of dissociation is often to form incomplete molecules called free radicals. These free radicals are very highly reactive and will set up a train of chem-

ical reactions that will continue until a stable chemical system is finally obtained.[98]

Gas Reactions

To understand a little better about the action of free radicals, let us consider the problem of ion production in gases. We will then go on to see how some of these factors hold in liquids.

The ion pair yield may be defined as the ratio M/N where M is the total number of molecules reacting and N is the number of ionizations in a gas.[26] However as noted above, excited molecules may also undergo reactions. Hence one might expect that the ion pair yield would be greater than 1. This is found experimentally in many gas reactions.[7]

On the other hand, there are reactions that occur in which the ion pair yield is less than one. One such reaction is the decomposition of ammonia. In such reactions as this, the low values of ion pair yield may be explained on the basis of recombination of the free radicals formed to give the original molecules back again, hence being removed and not counted as radicals formed.[2] It seems almost certain in gas reactions that for each ion produced in a gas, several molecules will eventually dissociate. This is another way of saying that ion pair yields of unity have no real significance. Because of the complicated secondary processes, the ion pair yield depends upon many variables, and even the walls of the vessel may exert variable effects. Another factor to be considered is the problem of back reactions. If molecules can be broken up by high energy radiation, they can also be formed. In other words, the decomposition and formation will be reversible in nature and the reactions may be made to go in either direction. On sufficiently long irradiation then, one would expect these systems to approach an equilibrium or at least reach a steady state in which the rate of the reaction in the opposing directions are equal and therefore no net change in ion concentration is observed. Sometimes this steady state lies very far toward one side of the reaction. For example, CO_2 decomposes very little under radiation. Also, with water vapor, some hydrogen and oxygen are formed but these molecules rapidly recombine. This recombination is thought to be accelerated because the molecules are attacked by free radicals formed in the dissociation of the water vapor.[2,98]

Liquid Reactions

Liquids differ from gases in many respects, but one elementary difference is that the molecules in a liquid form a "liquid structure". If an electron in one part of this structure is affected other electrons in other parts of the structure will show some response. Therefore molecules in liquid solutions are more easily ionized than molecules in gas solution. One would then postulate that for a given amount of energy absorption, more molecules would be affected in a solution than would be in a gas. Because there is no way to determine the number of ions and excited molecules formed on the irradiation of a liquid, the above statement must remain a postulation. Even in noncunducting liquids such as hexane or heptane where one can show conductivity after radiation proving that ions are formed, there is a continuously increasing current with increasing voltage and no limiting value is obtained.[2]

Irradiation of Water[7]

In water the situation is even less well defined. Water, as it is generally encountered with ion impurities, is a natural conductor. Hence the change in conductivity expected from radiation is completely masked. In addition to this, water can behave as though whole groups of H_2O molecules are hooked together as one unit, and these groups form an associated liquid that may act in the excitation process. About the best one can do is to assume that the energy to produce an ion is the same in water as it is in air.[7] These numbers cannot then be taken literally, but nevertheless are of value in that they would express the density of energy release along the track of the radiation.

Molecules of water in the liquid state, just as in the gas, dissociate into free radicals under irradiation. Materials dissolved in highly aqueous solutions react rapidly under x-rays. This indicates that a long-lived "activated water" is formed by the radiation and this "activated water" in turn brings the molecules into chemical reaction.[98] It is unlikely that active species other than the free radical would have a half-life long enough to reach all dissolved molecules in a highly dilute solution. The simple ion H_2O^+ which would be expected to be formed at least in part is very unstable under normal conditions and must dissociate into OH and H^+.* It is also true that the free electron ejected in the ionization to form H_2O^+ must react with water molecules to give free H ($H_2O + e = OH^- + H$). This is the same reaction that one obtains in normal electrolysis reactions.[7,98]

Because water may act as an associated liquid it is possible for groups of molecules to act together in the excitation process. This would make possible the direct decomposition to form stable molecules, and would lead to reactions like $2H_2O = H_2 + H_2O_2$.[1,2] Presumably such reactions are more likely with denser ionization. With denser ionization, radicals should be formed close together along the track of radiation. This would increase the probability of the radicals, reacting with one another to give hydrogen and hydrogen peroxide by such reactions as $H + H = H_2$ and $OH + OH = H_2O_2$. If the radicals are formed in high density, such reactions could occur before the radicals could diffuse out of the track and into the main body of the solution. It would appear then that solutions would behave as though two primary processes were occurring simultaneously:

$$H_2O = H + OH$$
$$2H_2O = H_2O_2 + H_2$$

So far this has been theory. What actually can be observed in the irradiation of water and water decomposition? Alpha particles decompose water with a yield of two molecules of hydrogen per 100 ev absorbed. Other heavy particle radiations that are somewhat less dense as ionizers (deuterons and pile radiation) also decompose water but with a yield smaller than 2. In all of these cases the apparent initial reaction is a decomposition of H_2 and H_2O_2. The peroxide would decompose to oxygen so the final reaction would appear to be the formation of gaseous H_2 and O_2.[2]

With x-rays or fast electrons there is a small amount of decomposition of water even in pure water. This decomposition slows down or stops when the pressure of hydrogen over the water reaches pressures of 1 or 2 cm of mercury. This would correspond to a concentration of just a few micromoles of hydrogen dissolved per liter.[2] The leveling off of this reaction can be explained by introducing the concept of the back reaction. The back reactions that occur would simply be the recombination of products into water, the original starting material. In light of this view the differences observed between alpha particles and x-rays are simply that the steady state concentration of products such as H_2, H_2O_2 or O_2 are much higher for the alpha particles, while with x-rays the back reactions have resulted in the formation of more water and destruction of the other products.

The mechanisms of the back reaction is fairly simply understood in terms of free radical theory. The free radical H must reduce H_2O_2 and the OH must oxidize the H_2 acording to the equations:

$$H + H_2O_2 = H_2O + OH$$
$$OH + H_2 = H_2O + H$$

These reactions constitute a self-perpetuating chain so that there is only one radical needed to reconvert many molecules of product into water.[2,7,98]

In partial summary then the irradiation may be understood in terms of two simultaneous primary processes. The products are formed by $2H_2O = H_2O_2 + H_2$ and are recombined by the radicals formed in the reaction $H_2O = H + OH$. When alpha particles are involved, the

*Free radicals will be written without a charge sign, while ions will include a charge sign. Hence H will be the hydrogen free radical and H^+ will be the hydrogen ion.

ionization along the track is dense, the radicals recombine before they can diffuse into solution and steady state of H_2, H_2O_2 and O_2 is high. When x-rays or beta particles are involved ionization along the track is small, radicals can diffuse before they recombine and the back reactions become important. As a result the steady state concentrations of the products is lower. If particles of intermediate energy release are involved, the steady-state concentration of products will be intermediate.

Irradiation of Water Plus Inorganic Solute

What has been said so far has been about water only. If one considers solutions, it is observed that the steady state pressure of products formed is greatly increased by dissolved substances. Even suspended glass will raise the steady state level of products. This is simply because dissolved substances react with free radicals and prevent them from reacting with the hydrogen peroxide.[2] Solutes capable of existing in either a reduced or oxidized state, say x and xOH, or x^- and x, may react in the following ways:

$$x + OH = xOH$$
$$xOH + H = x + H_2O$$

or

$$x^- + OH = x + OH^-$$
$$x + H = H^+ + x^-$$

In each set of reactions the net result is $H + OH = H_2O$. With the radicals recombining, the H_2O_2 is not broken down and hence serves as a product in high concentration.

Good evidence for the mechanism discussed is given in studies of x-irradiation of solutions of neutral bromide or iodide. In such studies it appears that the bromide or iodide is not itself oxidized by the x-rays, but apparently causes decomposition of water to H_2O_2 and H_2. This does not occur in the absence of the solute. This evidence may be explained if one assumes that the bromide ion suppresses the back reaction by reacting with radicals according to the scheme discussed above. In such a study the rate at which the H_2O_2 is produced is that with which it is formed directly along the radiation track, since no H_2O_2 would be destroyed.[2]

In the cases discussed, the inorganic ions had the superficial appearance of catalysts in the sense that they themselves were not changed. This is not always the case. Various reducing agents (AsO_3^{-3}, NO_2^-, $Fe(CN)_6^{-4}$) have been found to be oxidized in dilute aqueous solutions.[2] The interesting point here is that the yield is always the same independent of the solute concentration. When these results are compared to the experiments with bromide and iodide, it can be shown that the yield obtained in the oxidation is the same as the H_2O_2 yield with iodide or bromide solutions.

From a rather intensive analysis of the results of experiments in which aqueous solutions of both oxidizing and reducing agents were irradiated, Allen[2] has concluded that with x-rays at least 90 percent of the decomposition of water goes by the equation $H_2O = H + OH$. About 10 percent of the decomposition goes by the reaction $2H_2O = H_2O_2 + H_2$.

With this mechanism established by work with inorganic ions, one can interpret results of interest to the biologist. For example, inactivation of the enzyme carboxypeptidase in dilute solution is only 5 percent as large for alpha particles as for an equal amount of energy in the form of x-rays.[24] This reaction presumably results from the radicals formed. It may be concluded then that with alpha particles only a small part of the reaction occurs by the reaction $H_2O = H + OH$, and the main, effective primary step is $2H_2O = H_2O_2 + H_2$.

Irradiation of Water Plus Large Molecules

Since the biologist is very often concerned with large molecules, it should be of interest to see where the logic and reasoning that has been followed so far will lead when applied to large solute molecules. With small molecules the amount of reaction found is linear with dose. This can be expressed as $-ds/dr = G$ where G is the yield, s the concentration of solute and r the dose in kiloroentgens. When one is studying large molecules, it is necessary

to measure some functions that the molecule performs, if one is to see whether or not the molecule is active or affected. One such function of some protein molecules is enzyme activity. This activity is associated with some particular part of the protein molecule and makes the molecule behave as a catalyst. The principle part of the protein molecule reacts just as readily with the radicals after its enzyme activity is lost or destroyed. The rate of reaction of the radiation on such a system must still be independent of time, but the chance that the reaction will produce an observable enzyme inactivation is proportional only to the number of active molecules remaining so that the rate becomes $-ds/dr = G\ S/S_0$, where S_0 is the amount of material initially present. Upon integration this yields an exponential reaction-dose curve. The general rule that can be deduced from this is that for small molecules there is a linear dose-survival relationship and for large molecules there may be an exponential dose-survival relationship.

Before leaving this topic, it is desirable to list the possible products of ionization of water by ionizing radiations. Some examples of these reactions will be found from time to time in further discussion.

H_2O + radiation $\rightarrow$ OH + H
H + OH $\rightarrow$
H_2O —primary recombination
OH + OH $\rightarrow H_2O_2$
H + H $\rightarrow H_2$
OH + OH $\rightarrow H_2O + O$; $2O = O_2$
H_2 + OH $\rightarrow H_2O$ + H
H_2O_2 + H $\rightarrow H_2O$ + OH
H + O_2 $\rightarrow HO_2$
H_2O_2 + OH $\rightarrow H_2O + HO_2$
$HO_2 + HO_2 \rightarrow H_2O_2 + O_2$
HO_2 + H $\rightarrow H_2O_2$
$H_2O_2 + HO_2 \rightarrow H_2O + O_2$ + OH

Comparison of Direct and Indirect Theories of Action

The development of the concepts just discussed constitute the basis of the "indirect action" theory of ionizing radiations. This "indirect action" theory is based on the formation of an intermediate agent (activated water, OH radicals and H atoms) which in turn acts on the solute molecules. This now leaves us with the original concept of direct dissipation of energy within a molecule (the target theory) to be compared with the idea of energy dissipation through an intermediate.

The deactivation of the enzyme system that we have mentioned earlier could occur either by the direct absorption of energy by some specific loci in the molecule or by the action of an intermediate formed from the radiation. The exponential shape of the inactivation curve could fit for either mechanism. The exponential relation found for any one concentration of an organic solute does not alter the basic proportionality between x-ray dose and the effect. This basic proportionality must be varied by studying a series of solutions in which the initial concentration of solute has been varied. Only with experiments of this kind is it possible to decide whether the action of the radiation is direct or indirect.

Dilution Effect

If different initial concentrations are used for either an inorganic or an organic solute, it is found that the number of solute molecules changed for a given dose of x-radiation is independent of the initial concentration of solute. Saying this another way, the ionic yield (M/N where M is the number of molecules changed and N is the number of ion pairs formed) is independent of the initial solute concentration. This then means that the *percentage* change for a given x-ray dose is higher the more dilute the initial concentration. The converse is also true that the x-ray dose which produces a given percentage change increases with increasing initial concentration. As a consequence of this, one may expect that when a dilute solution of the enzyme is irradiated by an x-ray dose which is sufficient to inactivate the greater part of the enzyme, a concentrated solution would seem practically unchanged when irradiated with the

same dose of x-ray. This phenomenon is generally known as the "dilution effect."[26]

If the radiation were to act directly on the solute molecules without the benefit of an intermediate agent such as radicals, the proportion of solute molecules changed chemically would remain constant, that is, independent of the initial concentration.

Experiments with the enzyme carboxypeptidase,[23,24] for which the analytical method is very good, have shown that below certain low concentrations the radiations become less and less efficient the more dilute the solution.

Protection Effect

If at high dilutions the solute molecules were widely separated the radicals would have a better chance of colliding with each other than they do with a solute molecule, and protection would occur. However, if there were slight traces of impurities in the solution, this impurity could act as a second solute which would be in active competition with the enzyme for the radicals formed and protection would also occur. This would then reduce the effect on the enzyme for the radicals formed and in turn would reduce the effect on the enzyme molecules. This is similar to the effect seen in payment of stock dividends. If a given amount of money is to be distributed, there is less money for each stockholder as the number of stockholders increase. With radiation this competition will then be more effective the lower the concentration of the original solute relative to the impurity. This effect leads to, and in fact is part of the "protection effect" that is observed in solutions of two or more solutes.[26]

With two or more solutes in solution, all assumed to be able to interact with the radicals available, there is a competition between the solutes for the available radicals. It should be obvious from this that there would be fewer radicals for reaction with any given solute than there would be if that solute were present by itself. As a result of this, the radiation effects on each single solute in a mixture is reduced and the solutes appear to "protect" each other. Such protection varies with the amount of each solute present and also with the relative capabilities of each solute as an acceptor for the radicals.

In a sense, the exponential relationship between chemical change of carboxypeptidase and x-ray dose as mentioned earlier is an example of the protective effect. Actually, only one type of molecule was originally present, namely active enzyme molecules. By the action of radiation the originally active molecules lose their activity and become a second kind of solute molecule, inactive protein molecules. This second kind of solute molecule still competes for radicals, but the reaction is not measured, since the criterion of the radiation effect is enzymatic activity.

To illustrate the protective effect more completely, we should discuss some specific experiments.[24] The enzyme D-amino acid oxidase, like all enzymes, is a protein molecule that acts as a catalyst in a given reaction. The reaction catalysed by this enzyme is given in the following equation:

$$CH_3CH_2CHCOOH + H_2O \xrightarrow{\text{enzyme}}$$
$$\quad\quad\quad

process of the change oxygen is consumed and the system is said to respire. The activity of the system can be measured simply by measuring the amount of oxygen consumed. When the active enzyme acts on the substrate D-alanine (an amino acid), one can then measure the activity by simply measuring the uptake of oxygen. In this way the oxygen uptake of the entire system represents the activity of the enzyme system. If one now irradiates the prosthetic substance alone, and also solutions of the prosthetic substance at the same concentration, together with different concentrations of some protective substance (say a substance leucylglycine in which two amino acids are hooked together), and then introduces this irradiated substance into the enzyme system, it is seen that the oxygen uptake decreases with decreasing concentrations of the protective substance itself.

This experiment then shows the protective effect, and in addition it shows that the prosthetic group which is not an enzyme can be affected by radiation. The dilution and the protection effect have only recently been investigated. Experiments on biologically active substances carried out previous to the elucidation of these factors (some 10-15 years ago) may be complicated by the failure to consider these concepts.

For many years enzymes were thought to be too radioresistant to account for any of the effects of radiation, since such large doses were needed to cause any effects on the enzymes. As long as experiments were performed on impure extracts from tissues (an unawareness of the protection effect) and with too concentrated solutions (an unawareness of the dilution effect), the true radiosensitivity of enzymes was masked.[25]

The use of crystalline purified enzyme in recent times has shown that quite small doses of x-rays of the order of a few hundred roentgens could, under certain conditions, partially inactivate the enzyme.[10]

Abnormal Yield-Concentration Relations

Concepts of the indirect action of radiation can be deduced from the inactivation of an enzyme and the oxidation of ferrous iron. The characteristic feature of the indirect action concept, namely that the yield is independent of the concentration over a wide range of concentrations, does not always hold. A number of reactions have become known in which the yield is very much dependent on the concentration of the solute. Examples of such reactions are the inactivation of trypsin (a digestive enzyme) and the deamination of removal or the amino (NH_2) group from amino acids.

If the amino acid glycerine is irradiated in solution, the ammonia liberated increases continuously with irradiation. There is no sign of leveling off, even at the highest concentration of amino acid, its limit of solubility.

This deamination or ammonia formation rises to an ionic yield (M/N) of 2.9.[25] This is to be contrasted with the constant ionic yield of the enzyme carboxypeptidase of 0.18 down to much lower doses. It should be recalled that in the case of carboxypeptidase it was concluded that all radicals reacted with the enzyme molecules rather than with themselves at all concentrations above 0.1 percent protein.

With the amino acid serine it appears that there is a tendency for the yield-concentration curve to level off at higher concentrations.[25] The explanation of the difference between the radiation effect on deamination and the inactivation of an enzyme is simply not understood at present. However, it may be useful to discuss some of the factors that may be involved.

The irradiation of amino acids is characteristic for its high ionic yield, that is above 1. For enzymes the ionic yield is low, being approximately 0.18 for carboxypepidase while for trypsin in a 1 percent solution it is about 0.01.

Since it appears that for large biological molecules the maximum ionic yields are much lower than for deamination reactions, we may venture a guess that collisions of active radicals with large solute molecules do not always lead to the specific change (loss of enzyme activity) that we may be investigating.

It has been suggested by Dale[26] that it may be necessary for there to be a special orientation of the solute molecule and the radical to achieve inactivation. If this is so then any collision of nonoriented partners may lead to elimination of the radical and to some change in the solute molecule but not to inactivation. It would appear therefore that the shape of the yield-concentration curve is linked to the fate of the radical. Any elimination or destruction of a radical through reactions in irrelevant regions of the solute molecule will favor the attainment of consistency of the ionic yield down to low concentrations of the solute.

If there are collisions of the radicals with solute molecules that leave the two partners unchanged, it will favor recombination of the radicals. This would result in a curve that shows a shift to a constant ionic yield at higher concentrations of solute. It should be pointed out that the orientation concept is only one of what may be several ways to interpret the results.

While the considerations we have made may be relevant to the shape of the yield-concentration curve, they certainly do not explain why the ionic yield of deamination is so high.

We frankly do not know the answer to this but we can guess. If every collision of any active radical with a solute molecule led to a chemical change that could be detected, the number of changed solute molecules would equal the number of radicals formed. From this one could decide how many radicals can be formed by any particular dose of radiation. Actually, the situation is far more complex. Back reactions and chain reactions can interfere.

The estimate has been made that three radical pairs can be formed from the absorption of an energy corresponding to the production of one ion pair (approximately 32.5 ev). Some estimates have put the value at three. This would include radicals formed by excitation and charge neutralization as well as by ionization, and would appear to be the upper limit possible. In this way the ionic yield could be three if only one type of radical is involved and would be six if two types are involved. This assumes that no radicals are lost by recombination or back reactions. Yields of very high order of magnitude can also be explained in terms of chain reactions.

Summary of Comparison

In partial summary we can now compare the direct and indirect action of radiation. In general, one might say that the indirect action theory is a generalized form of the direct action or target theory.

The target theory in its narrowest interpretation requires that the critical ionization from the radiation must occur in or very near a critical molecule within the biological system considered. The indirect theory simply enlarges the "target" to the whole system under investigation. In this theory radiation forms an active molecule which in turn affects the critical structure in the biological system.

Probably both modes of action occur. However, the indirect theory is more flexible in its interpretation and need not require an ionic yield of 1, as does the direct theory, to obtain an exponential dose-response curve. When the active radical is formed near the critical structure it will affect, it appears that the differences in the two theories disappear. This is only superficially true, however. For example consider the experiment in which fracture of a chromosome results from the action of the radiation. If a direct hit by an irradiating particle is needed for the rupture, very little is learned beyond the fact that the rupture has occurred. However if the break ocurs as a result of a series of chemical or physical reactions triggered by the radiation, an understanding of the mechanism might well lead to a better understanding of chromosome structure and chemical composition.

LINEAR ENERGY TRANSFER[102]

When a cell or organism is exposed to any high-energy radiation, ions and excited molecules are clumped or localized along the track of the particle. The effect then has to be considered as a parameter in any consideration of the mechanism of action of radiation.

The volume of the tracks formed constitute a very small percentage of the cell volume even when high doses of radiation are received. The properties of the ions and excited molecules along the track are independent of the properties of the high-energy particle that is used and hence are considered the same for all types of radiation. However, the linear spacing of the ion pairs and excited molecules along the track varies widely with the velocity and the charge of the particle considered.

When gases are considered, one generally refers to the ion pairs formed per unit length of track as the so-called "linear ion density." In tissues this quantity is not so easily determined. One must rather determine the ratio of energy released per unit length of track to energy gained by the tissue per ion pair formed. As has been discussed earlier, this latter quantity has never been accurately determined and the best one can do is to assume it is the same as that found in air, namely 35 ev/ion pair.

If one considers only the ions formed in tissue as a result of irradiation, a rather limited and inaccurate impression is obtained, since all excited molecules and free radicals are not considered. Therefore it appears to be preferable to consider the energy transferred to tissue rather than the number of ions formed. Such energy transfer is generally refered to as linear energy transfer (LET) and is expressed in thousands of electron volts per micron of tissue (kev/μ). This type of unit would then serve as a unifying concept that would permit consideration of all types of radiation under one theory.

The linear energy transfer along a particle's path varies as the square of its charge. Therefore, the LET from an alpha particle is four times that from a proton, deuteron or electron of the same instantaneous velocities. The LET also increases as the particle's speed decreases because of the "Bragg effect."

In attempting to use the linear energy transfer experimentally, one has the choice of two general methods for obtaining variation in LET.

The first method is called the "track segment method" while the second is the "track average method." The track segment method is so called because one uses only a segment of the radiation track where the spread of LET is small. This, of course, requires biological samples that are small as compared to the range of the particle used because the beam of particles must transverse the biological specimen and use only portions of the over-all track.

The second method allows for the entire track to be spent in the specimen. The energy transfered along the entire track is then averaged over the length of the track. This method results in a wide range of LET values.

With equipment now available the LET can be varied continuously from about 0.25 kev/μ (a single charged particle traveling at the speed of light) to about 260 kev/μ (at end of an alpha particle track). There is little chance to extend this range toward the lower end since it appears that the theoretical limit is about 0.2 kev/μ. On the upper end of the range one may accelerate carbon ions whose LET is about four times that of the alpha particle. Fission fragments have a

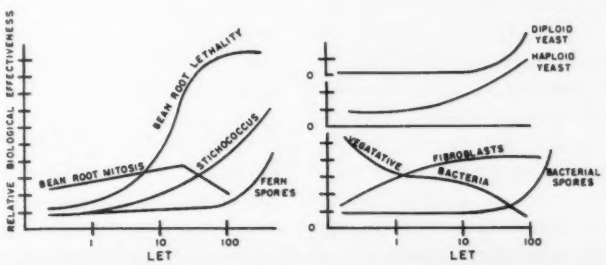


Fig 9. Effect of LET on various biological systems adapted from reference (102). Not to scale.

LET of about 6000 kev/μ and may be used for certain types of experimentation.

It should be pointed out at this time that no general theory of the radiobiological operations of LET has yet been published. Because it is a very complicated subject this is perhaps not surprising. Even in the absence of knowledge of the role played, however, it is of interest to see what factors are of importance when radiation effects are considered in terms of LET.

The effect of LET on various biological systems can be shown in graphical form (Fig. 9).

From these graphs it is clear that as the LET increases, the relative effectiveness of the various radiations may remain unchanged, may increase, or may decrease depending upon the nature of the irradiated object and upon the effect studied.

In most cases where LET had no effect, the radiations differed in mean LET by a factor of 5 or less. Bacterial spores and fern spores and some other forms are independent of LET as it varies by a factor of 50 or more but there is an effect if the LET variable is pushed higher.

This would seem to indicate that practically all radiobiological responses would be found to be dependent on LET if the range of this variable were wide enough.

Many additional examples could be shown for the effect of LET in biological systems. The number shown, however, are sufficient for our purposes. The differences in the curves given indicate that at least five distinct mechanisms are involved for the nine different effects shown. However, four of the curves (yeasts and spores) are quite similar, thus indicating that the same or very nearly the same mechanisms may be operating in all these cases. For those interested in the problems of LET, it is necessary that future investigations supply additional effectiveness curves over a wide range of LET values. In this way it may be possible to see if there are a relatively few or a definitely large number of mechanisms operating when biological tissues are irradiated with different forms of energy.

BIOLOGICAL ENDPOINTS

Radiation is a constant part of the environment of all biological systems. At a minimum life is bombarded by cosmic rays and from naturally occuring radioactivity both in the body and in the atmosphere. All of these factors combine to form a natural "background" radiation which at sea level corresponds to an average x-ray dose of about 0.13 r/year. In addition there is a normal body burden of radioactivity in animals and plants. In humans the basal level of radioactivity is about the equivalent of 1.03×10^{-8} g of radium.

While this "background" radiation is constantly with us, it is negligible when compared with the intensity of radiation encountered either in biological experimentation, when nuclear accidents occur or when x-ray therapy is used.

When radiation is applied to an experimental system, single exposures at relatively high dose rates are grouped under the term *acute.* Multiple exposures at low dose rates are grouped under the term *chronic* irradiation. Obviously the divisions between the two groups is completely arbitrary and depend upon the choice made by the individual experimenters.

All living tissue can be killed if a high enough dose of radiation is used. With some forms such as micro-organisms the amount of radiation required to do this is enormous, amounting to hundreds of thousands of roentgens for immediate death. With conventional equipment such a dose would require several hours so of course the term "immediate" is only relative. Nuclear detonations however, make it possible to produce sufficient energy to result in instantaneous lethality. These very high dose levels literally fry any living tissue, thus disrupting all physiochemical mechanisms.

Specification of Lethal Endpoint

Lower doses of radiation initiate a progressive deterioration in the irradiated tissue which may not be complete for days or even weeks but which will eventually account for the death of the material exposed. In the sublethal dose

range there is a delay before the full impact of the radiation is observed. This delay is inversely proportional to the radiation dose. The lethal dose of radiation may therefore be measured in a variety of ways and we may summarize these in a relatively simple manner:

1. By death of the entire cell population or organism
   (a) immediately (by end of exposure).
   (b) delayed, independent of interval between exposure and death provided the degenerative process is progressive and affects all members of the population.
   (c) delayed but within a specified time.
2. By death of 50 percent of the exposed population (referred to as median or mean lethal dose, half lethal dose, or LD_{50})
   (a) immediately (by end of exposure).
   (b) delayed, independent of interval between exposure and death.
   (c) delayed but within a specified time.
3. By a lethal endpoint in some specified percentage of the population with time measured to some stage of development.

If a given population of animals is irradiated with a high dose of radiation there will be a "normal" (Gaussian) distribution of the deaths of the animals. Therefore some will die early while others may never die. Hence, unless very high doses of radiation are used, there is extreme variability in what is to be called the "lethal dose." To avoid this complication it has become expedient to decide on some fraction of deaths that is aceptable (usually 50 percent) and then specify the time at which this number must be reached. Hence one may refer to the dose of radiation that will kill one half of the population in 30 days. This is written as LD 50/30.

In the case of certain kinds of material such as developing embryos, and even this system is inadequate to describe the effects, the results may be ambiguous if a time limit only is specified. This is so because such systems are undergoing very rapid changes which are influenced by such parameters as the temperatures at which the experiments are done. In these cases it is better to specify a particular stage of development to be reached before death, instead of merely stating a time interval.

Specification of Non-Lethal Endpoints (Reversible Reactions)

Reactions to radiation in which permanent damage is done are called irreversible changes. However all changes are not irreversible. Radiation damage is followed by a process of repair. How successful this repair is depends upon how much damage has been done or in other words how much energy has been absorbed. After very small doses of radiation, most tissues recover fully and behave like normal tissue. This is seen in the irradiation of growing tissues. Here cell division is simply delayed and then resumed in a manner such that no change can be observed. After larger doses, recovery may appear to be complete but there may be some minor changes in the character of the tissue. This type of an effect is seen in the experiment in which irradiation of the skin of a rat causes temporary baldness. The hair will grow in again but it may be another color, for example, black hair replaced by white.[9] In man cases are known in which white hair has been replaced by black.[89] These changes are limited reversible reactions and the changes may or may not be temporary. If one uses still higher doses of radiation, recovery from the effects of radiation may appear to be complete until some new stress is applied in the form of either more radiation or some other injurious agent. The tissue then seems to be unable to resist this stress, and completely breaks down and shows changes which are of the irreversible type. This type of reaction is sometimes called a conditional reversible reaction. This particular effect is of great importance in radiotherapy, since many times a person may not disclose the fact that he has had previous treatment. Then, if further radiation is given to the same part as previously exposed, the consequences might be serious, although to all outward appearances the tissue is normal and has recovered completely from all previous treatment.[89]

When tissues appear to recover from radiation damage it is often difficult if not impossible to tell whether the individual cell has recovered its *status quo* or whether cells adjacent to the damage have simply accelerated their activity to compensate for the damage. Most recovery from radiation damage appears to be accelerated recovery on the part of non-affected cells.

These examples show that one should use caution with such expressions as "the biological effects of radiation." A given cell may differ in its sensitivity to radiation according to its water content, its metabolic activity, its stage of division, and its stage of growth, as well as its age. Quite small injuries may lead to death of a cell under some circumstances while the same dose produces no permanent change under other circumstances. The living cell is capable within limits of adapting its behavior to changes in its environment including those changes brought about by radiation. This may be done by simply reducing its normal activity and thereby altering its susceptibility to further radiation. Then if the radiation is stopped, the cell will regain its normal state completely, including its original susceptibility to radiation. However, it is also possible, according to the timing and the circumstances of the radiation for the susceptibility to be increased or decreased upon recovery. Thus a series of exposures may, according to the spacing do equal or more damage than the same total dose given in a single exposure.[89]

SOME RADIOBIOLOGICAL GENERALIZATIONS

It is possible to draw certain generalizations concerning the effects of radiation on living systems. As with all generalizations, exceptions make it impossible to use them for anything except a "rule of thumb." Nonetheless such generalizations sometimes help an over-all picture of a possible mechanism. Toward this end, some generalizations are given.

(1) Simple organisms, particularly one celled systems (protozoa) are resistant to radiation.

(2) Complex organisms are more easily affected by radiation than are simple ones.

(3) In a given organism, irradiation of a large volume leads to greater damage than does irradiation of a limited volume. This is apparent if one considers that single organs of the body can tolerate ten times the dose of radiation that would be lethal if it were administered to the whole body of the organism.

(4) As a given organism becomes older, it becomes less sensitive to radiation. Care must be exercised if this generalization is applied to rapidly developing systems such as an embryo. In these cases the damage done may be related to the state of development rather than to age *per se.*

(5) In a mature organism the radiosensitivity of an organ or tissue is dependent upon its rate of biological activity at the time at which it is irradiated. Because of this radiation may be used either to produce inflamation or to sooth an existing inflamation. The response of the tissue will depend upon the state in which the tissue existed before it was irradiated.

(6) Healthy cells are more resistant to radiation than are unhealthy cells. It is on this basis that cancer can be treated *in situ* in an animal.

(7) The condition of a tissue observed after irradiation is dependent not only on the damage done by the radiation but also upon how much recovery has occurred in the tissue. Because of this one may often expect to find a variation in biological effects because of individual variation of tissues to both the damage done and the rate at which the tissue recovers from damage.

CHOICE OF A RADIOBIOLOGICAL SYSTEM

Studies in radiation biology may be grouped under two general philosophical approaches. One approach is to unravel the mode of radiation in general. This approach is designed to examine the effects of radiation on any and all types of tissue or material and has as its endpoint the increase in general knowledge that

will lead to an explanation of how radiation acts on all systems.

A second general approach is not concerned with any such ambitious undertaking, but rather attempts to explain what might be expected when the human is irradiated. For obvious reasons this study cannot be undertaken directly. Therefore it is necesary to study systems other than the human and then relate this knowledge to the response of human tissue. It is possible to conceive of a nonhuman tissue that will respond to radiation in the same way as does human tissue. If such a tissue could be found, it would then be possible to carry out a systematic investigation of the biological effects of radiation and from this explain how the human would respond. To find such a tissue would be a piece of luck indeed. In view of such a model system, different observers have chosen different specific tissues for systematic study and have contented themselves with the investigation of some one characteristic that might be related to the response of human tissue.

Utilizing either one or both of the general philosophies noted above, a number of systems have been investigated. Each system seems to possess both advantages and disadvantages as biological indicators. For example single celled protozoan systems or bacteria require very high dose levels, out of context with the response of human tissue. Plant cells have yielded much interesting information but are only remotely related to human tissue. Use of more complex experimental systems such as mice, rabbits or dogs possesses the complication that they represent interdependent organ systems that yield results that are no easier to interpret than are those observed with humans. Further, many effects of radiation appear to be species dependent and results obtained with lower mammals are only indirectly applicable to the human.

If one is to choose a specific tissue for study, it is best to begin by selecting a relatively simple tissue, that is either human or not too distantly related to human tissue, which can be irradiated under very carefully controlled conditions and which is at the same time reasonably sensitive to radiation.

Several systems meeting these requirements have been investigated. Two such systems are human cells of a non-neoplastic origin[77] and fibro-blasts from the connective tissue of an embryo chick or mouse.[89] Both of these tisues can be investigated as a simple hanging drop tissue culture. In such a preparation the response of cells to radiation can be observed under simple conditions. It should be remembered that the response may well be modified when irradiation is done under the more complex condition of a total organism. The use of tissue culture, however, permits particular radiation effects to be picked out and recognized independently. This is of considerable help in trying to understand the composite picture seen in *in vivo* irradiation.

As with any model system there are both advantages and disadvantages to working with tissue culture preparations. The chief advantage lies in the simplicity of the system. The individual cells are all potentially dividing cells and their activity is not subject to rhythmic changes as in the case of some other tissues. During the period of most active growth less than 5 percent of the cells are actually dividing at one time but none the less that is a relatively large number of dividing cells at any one time. Tissue cultures are in effect a large population of cells in the resting state interspersed with dividing cells, all growing under conditions which eliminate the complications due to either nerve or blood supply or to the reaction of the organism as a whole. The lethal effects of radiation or other injurious agents for the culture can be recognized by the loss of mobility of cells. Sublethal effects can be studied by observing changes in behavior of individual cells and some of these changes can be expressed quantitatively, e.g., the diminution of cell division or the occurrence of degeneration among cells of the zone of outgrowth.

The fact that one may not get the same effect when tissue cultures are irradiated as one

does when studying *in vivo* irradiation is really no argument against the use of the tissue culture system, since one of the principle objects of using the method is to eliminate some of the numerous unknown factors which so often hopelessly complicate the tissue *in vivo*. Naturally, therefore, we would expect different effects. It must always be remembered, however, that the work *in vivo* gives only part of the story and it should not be interpreted or treated as though it were the whole explanation.

Effect of Dose Level

Before it is possible to use the information derived from a tissue culture "model system" to compare with *in vivo* experiments, it is necessary to understand the response of the tissue to the radiation dose range of interest. This range of interest ranges from slightly less than 100 r to levels of the order of magnitude of 120,000 r.

With doses of the order of 120,000 r, all cells in a tissue culture preparation are dead by the time the administration of the radiation is complete. Doses of radiation at somewhat lower levels result in a delayed lethal effect in the culture. This is to say the interval between exposure and death increases as the radiation dose is decreased. In the dose range that results in delayed lethal effects, large numbers of cells are degenerate by the end of the exposure, although there are also many cells that appear normal. To determine if these latter cells are truly normal, a fraction of the culture can be removed to a fresh nutrient solution which has not been affected by the irradiation. If this process is carried out, repeatedly, the apparently normal cells will be found to degenerate and die. This fractionation process is called subcultivation, and the entire process in this instance reveals the delayed nature of the lethal effect. The degenerative changes that occur within the cell before death affect both the nucleus and the cytoplasm. Giant cells may be produced, the number of chromosomes present may be different in the cells that divide and physical chemical changes occur such as increases in acidity of the cell thus disrupting the normal funtions of the cell.

If the dose of radiation is reduced to about 15,000 r some cells of a tissue culture preparation will survive and go on to divide. [89] However in this dose range the response is not always the same; sometimes the entire culture dies out. This is the response that would be expected if the dose level used is close to a borderline condition where normal biological variability of the culture becomes a determining factor.

The dose levels of radiation discussed so far are very high. At these levels radiation appears to act indiscriminately and very little can be learned about how radiation acts at the level of the growing cell.

To understand how radiation can affect cells without totally disrupting them, it is necessary to start at low radiation dose levels and gradually increase the dose in a series of experiments. Such experiments allow the effects due to radiation to appear one at a time at their threshold levels and this in turn permits a more rigorous analysis of the results.

Doses of radiation somewhat below 100 r result in a simple delay in the time of division of the cells in tissue culture for both human tissue[77] and fibroblast tissue from the embryo of the mouse.[89] The reason for the delay in cell division has not yet been explained satisfactorily. The delay in division is only a temporary diminution in the number of dividing cells and not a complete blockage. The cells that had been affected do not degenerate and after a short interval go on with the division cycle in the same way as the cells that showed no effect of the radiation. There results an increase in total cell count at this time with the mitotic count rising sharply. This mitotic count will remain high while the cells are undergoing a compensatory mitosis (accelerated cell division). The cells then return to normal. This compensatory mitosis has been demonstrated not only in tissue culture but also in recovery of corneal epithelium tissue in the eye of the rat.[35] One suggestion to explain the accelerated

mitosis is that the cells may divide synchronously following the radiation induced block and the cells are simply catching up with their normal division cycle.

When the dose is elevated above the level just discussed, the return of mitotic activity after the initial fall is accompanied by the appearance of degenerative cells. The number of degenerative cells reaches a peak a few hours after the radiation. These degenerating cells are sometimes recognizable as dividing cells showing that the radiation in some way has led to the degeneration when the cell attempted to divide.[89]

If one determines the number of degenerating cells and graphs this wave of degeneration as a function of duration after exposure, the degeneration is found to occupy the same position as does the wave of compensatory mitosis in the samples irradiated at the lower level.

Such an analysis as this permits one to distinguish degeneration following high dosage (several thousand r) which acts indiscriminantly as a lethal agent to any cell from that radiation at a much lower level (a few hundred r) which is linked to cell division.

The time delay in recovery of mitotic activity is dose dependent. The minimal time delay is about 80 minutes.[89] If one uses a dose that is sufficiently large to keep mitosis at a relatively low level for some time before rising again, the appearance of degeneration is correspondingly delayed. As the dose of radiation increases from a low level, the total count of degenerative cells increases. This means the wave of degeneration gets bigger while the wave of mitosis becomes smaller and smaller until it virtually disappears. With each increase in dose the mitotic activity is delayed and with it the onset of cell degeneration.[89]

It should be apparent from this that when searching for degenerative changes after irradiation at different dose levels, it is necessary not to confine the observation to some limited, specific time after exposure, but to observe the material over a prolonged time so that any delay in the onset of degeneration is not mistaken for its absence.

It would appear from what has been said so far that radiation can affect cells by an indiscriminate destruction of the cells, or it can affect mitosis and result in cellular degeneration of some of the cells. High dose levels result in generalized destruction. Low dose levels result in cellular degeneration.

Radiosensitivity

A great deal of attention has been paid to radiosensitivity of tissues in terms of cell or tissue degeneration. The possibility of some relation between mitosis and degeneration has been suspected since about 1906 when Beryonie and Tribondeau[12] summarized some of these radiobiological observations into the form of a "law." This "law" stated that the radiosensitivity of cells is in direct proportion to their reproductive activity and inversely proportional to their degree of differentiation. Such a statement applies only to a tissue in which the orderly process of cell division and cell differentiation is taking place and should not be applied to all kinds of tissues indiscriminately. It apparently applies to normal tissue in which the differentiated cells are the oldest cells and are incapable of further division.

One should remember that in a given tissue where there are actively dividing cells, at least one of the daughter cells from each cleavage remains undifferentiated and capable of further division. Otherwise the tissue would die out and there would be no further supply of cells to undergo differentiation. Since we do not know at this time why approximately one-half of the cells differentiate, it must be assumed that each daughter cell has the option of dividing or differentiating. Radiation may well play a role of disturbing this balance, i.e., forcing more cells to differentiate rather than divide. If this is so, the use of cell degeneration as a criterion of radiation damage would represent the minimum of the effect of radiation on the system.

The use of a simplified system such as a tissue culture without the complication of dif-

ferentiation of cells, permits the experimenter to deal with radiosensitivity in simple terms of a decrease in mitosis or an increase in cell degeneration as we have seen. The question that still remains is the relative sensitivity of the mitosis as compared to the resting cell, or in other words the radiosensitivity of the cell in the different stages of the division cycle. Much work is still needed to elucidate this problem. At present it would appear that those cells just ready to divide may show the effects of irradiation while those that can rest some time before dividing may be able to repair themselves and hence recover from the irradiation.

Irradiation of More Complex Systems

If one wishes ultimately to understand the results of the irradiation of *in vivo* systems, more than simple nondifferentiating systems must be studied. Systems that are undergoing growth and development must also be investigated. One such system is the developing embryo.

Ionizing radiations affect embryos of all species including man. The nature of the damage that occurs depends upon the stage of embryological development at which the irradiation takes place. In rats and mice malformations of the embryo may occur with radiation doses as low as 25 r.[43] It would appear that response to this dose level of radiation also applies to other mammals including man.

The primary response of the mammalian embryo to radiation is destruction of the primitive cells (nonmitotic cells). As the embryo develops, these cells appear in each of the different organ systems as each system is developing. Therefore radiation applied while the nervous system is developing will result in malformation of the nervous system; that applied while the circulatory system is developing will result in malformation of the circulation system and so forth.[15]

Since the embryo is in a state of very rapid growth, one would expect that repair processes would also be rapid. Consequently once damage is done repair processes are initiated rapidly. Hence the final result of irradiation of an embryo is a function of the amount of radiation, the time of radiation, the initial damage incurred and the recovery.

It is possible to compare radiation effects on tissue culture cells with those in an embryo by use of an experimental system in which chick embryos are explanted at different stages of development, irradiated and then observed.

Experiments on chick embryos explanted just after the establishment of the circulatory system shows that the variation in mitosis is very similar to that seen in tissue cultures. However, if irradiation is carried out at a stage before the establishment of the circulatory system one sees a greater and more prolonged diminution in mitosis.[89] Apparently the presence of an intact circulatory system allows for a more rapid recovery of the radiation damage because the toxic products of irradiation can be carried away by the circulatory system. The explanation given seems to be augmented by experiments in which the dose level is increased to a level which causes the reduction in mitosis to be followed by cell degeneration. The degeneration that is observed is the result of the direct action of radiation upon the cells and is regional in the sense that it is restricted to areas where cell division is found normally. However, if the dosage is raised to about 1000 r where the circulatory system is affected, the degeneration that follows is enhanced by the generalized destruction which always follows any interference with the blood supply.[89] If one affects a sufficient number of blood vessels, it may very well lead to killing the chick embryo even though the dosage is still far below the massive lethal dose which kills by a *direct* indiscriminate action on all the cells of the body.

In partial summary, it should be pointed out that in many cases there is apparently a close similarity in biological behavior after low dosage of radiation whether the experimental material is exposed *in vivo* or *in vitro*.

IRRADIATION OF ORGAN SYSTEMS

Once one has obtained some understanding of the *in vivo* and *in vitro* irradiation studies, the question naturally arises as to how biological effects of radiations are modified when complex tissues are irradiated. One also must know how one tissue differs from another in its response to a comparable dose. This question is particularly pertinent when one approaches the problem of the effect of radiation on humans. The tissues or systems that appear to be most affected in the human are (1) the blood, (2) the skin, (3) the digestive tract and (4) the reproductive system including the genetic cells. A minimum understanding requires a knowledge of the effects of radiation on these four systems. To this end each of the four systems will be discussed in some detail.

Blood and the Circulatory System

General Remarks

The two circulating fluids of the body; namely, the blood and the lymph, are carried throughout the body by two closed circulating systems. The blood is propelled by the heart and the large arteries through a system of arteries and arterioles to the capillaries. At the level of the capillaries some of the fluid component of the blood passes through the vessel wall, bathes the surrounding cells, and is collected from the tissues by the lymphatic system. This fluid is then returned by the lymphatic system to the veins where it again becomes part of the blood.

The movement of the blood in the arteries is maintained primarily by the ability of the arteries and arterioles to contract. The vessels of the lymphatic system also contain contractile tissue. In addition they are supplied at intervals with valves that prevent reversal of flow of the fluid. The veins of the body are not contractile tissue but must rely upon a valving system similar to that found in the lymphatics to control the direction of flow of the fluid.

There is a significant amount of body space used simply for the transport of fluids about the body. In fact vessels of both the blood system and the lymphatic system are almost certainly going to absorb radiation whenever any part of an animal is irradiated.

Both the arteries and the veins have a structure that is complex. If one views a cross section of one of the vessels, one can observe that the innermost cells are flattened cells that form a lining (endothelium) of the tubule. Since the blood is constantly moving over these cells, they experience considerable wear and tear and therefore must be replaced fairly frequently. This replacement occurs by cell division of reserve cells. Immediately outside of this lining of cells is a layer of connective tissue and elastic fibers. It is this layer of cells that gives resilience to the blood vessel. Adjacent to this second layer of cells one finds first a muscular coating surrounding the vessel and then more connective tissue.

The structure of the capillary vessels is markedly different from that of the arteries and veins. Capillaries are composed of only a single layer of cells and this layer is continuous with the inner layer of the larger vessels.

Effects of Irradiation on Blood Carrying System

Penetrating radiation has an injurious effect upon the tissues which compose the heart and the blood vessels. This is an effect on the blood system, that is, of course, completely apart from the effect noted on the cells and circulating fluid. The injury to the blood vessels is a regional destructive effect that is dependent upon the volume of the tissue involved. Under certain conditions it is possible for blood vessels damaged by radiation to be replaced by small collateral channels that serve the same area as did the original vessels. These small channels enlarge to take the blood flow required to provide nourishment for the surrounding tissues. Repair of this form occurs only if radiation damage has not been too extensive, and is referred to as an "indirect effect of radiation" to distinguish it from the effects resulting from the direct action of radiation on the tissue.

Sensitivity of the Heart. The heart is generally termed radioresistant. However, it should

be remembered that the heart and the larger vessels are supplied with a miniature blood supply of their own and it is possible for these smaller vessels to be affected independently of the heart tissue. The heart tissue itself is very resistant to radiation and will continue to beat *in vitro* after irradiation with 500,000 r. The heart tissue has the same kind of resistance *in situ*. This resistance has been demonstrated where accidental exposures (lost radium needle) or radium have resulted in doses of several million r without stopping the heart.[89]

Sensitivity of Arteries and Veins. If arteries or veins are irradiated with relatively high doses of radiation, the first response is similar to that observed in a tissue culture; namely, mitosis is stopped and cell destruction may follow. Since the inner linings of cells in the vessels are constantly being worn away and must be replaced, inhibition of mitosis may lead to destruction of an entire network of vessels. If damage is not too extensive, nonaffected cells proliferate to constitute a form of repair. As with the repair processes in simpler systems, over-compensation can occur. Since this over-repair is in the interior of the vessel, the thickening of the lining will reduce the diameter of the vessel and obstruct the flow of blood.

If the radiation intensity has been sufficient to damage cell layers other than the lining layer, recovery of the connective tissue will predominate in the repair process.[89] The normal balance of the tissue layers is changed in this way and the permeability of the vessel wall is altered. In this state, fluid passes out of the blood vessel and swelling and edema are observed in the irradiated areas.

In short the specialized tissues of the blood vessel walls are replaced by scar tissue. This scar tissue may then serve to transport the blood and normal function is preserved if new stress is applied.

If one irradiates normal cells *in vivo*, one finds that the action of radiation on mitosis occurs at lower doses than that which affects the walls of the blood vessels. Mitosis in body tissues is affected by doses of radiation of less than 100 r. Through the dose range up to 1000 r the effect of irradiation on mitosis is qualitatively and quantitatively similar whether irradiation occurs *in vivo* or *in vitro*.[89] Under *in vivo* conditions any cell destruction that occurs up to about 1000 r has strictly a regional distribution and is limited to the parts of the tissue where cell division is going on. At doses over 1000 r given in a single dose the radiation affects cells composing the walls of the blood vessels. The damage that results is restricted to the area supplied by the blood vessel. Within this affected area the damage that occurs is indiscriminate and affects all cells whether they are dividing cells or not.[89] If collateral circulation is established rapidly the damage from the radiation may be checked ultimately.

As long as the circulatory system remains intact its action helps recovery from any direct effects of radiation on the tissue. Once the circulatory system itself is involved in damage then the direct effects of radiation are enhanced by the indirect destructive effects which result from loss of the circulation.

Sensitivity of the Capillaries. The capillaries represent the most radiation sensitive part of the circulatory system. The normal capillary is only slightly larger in diameter than is the red blood cell. Hence, even slight contraction of the capillary will result in a block that will stop the flow of blood. The state of permeability of the capillaries is affected by numerous factors including chemicals, pressure, temperature and drugs.[93] Radiation is simply another factor that exerts an influence.

Irradiation of the capillaries is followed by a marked dilation. This action is probably the result of histamine release following injury of the cells by the exposure. The effects on the capillaries for doses up to 600–700 r are reversible and the vessels eventually return to their normal size. Doses above 700 r cause the permanent dilation of the capillary wall with the loss of resiliency in the wall.[89] This rigidity then results in permeability changes in the capillaries. If the damage is not too extensive

new capillaries bud out from the existing vessels and this constitutes a form of repair.[56]

Irradiation Dose Rate

One phase of irradiation we have not mentioned so far is the effect of rate of dose administration on biological response. This effect can be demonstrated if one explants an 8-day chick embryo into a watch glass so that he can observe the vessels that run between the embryo and the yolk sac. The actual blood cells can be observed in this preparation. If now a dose of gamma rays of about 1500 r is given there is no effect seen at first but after a lapse of 60 min the blood cells can be seen to adhere together gradually producing a blockage. This block increases the pressure in the vessel behind the block and the vessel eventually ruptures releasing blood into the tissue. If this experiment is repeated at different dose rates, one finds that when the intensity of irradiation if of the order of 10 r/min the total dose which just produces the above described effect is minimal. Below 10 r/min the total dose must be increased to over 1000 r to produce the effect. Above 10 r/min the effect of intensity of dose is less marked.[89]

Other biological functions have been shown to respond in the same general way. Mitosis or mitotic activity in tissue culture seems to follow the same general pattern. Here it is necessary to measure the dose required to produce a given fall in cell division. This value of dose can then be plotted against dose rate. While the general response is the same, the absolute level of dose required to produce the mitosis effect is about 1/10 of that required for the circulatory effect.

It would appear from such experiments that for some types of biological responses the efficiency of the irradiation is dependent upon the rate at which energy is absorbed. The mechanism involved in this action is not understood at present. However, the total picture is probably very complicated and will require consideration of repair processes as well as initial damage in a final explanation.

Constitutional Effect

When any part of the body is irradiated and cell destruction occurs, the products of this cell destruction are carried to various parts of the body by the blood stream. Translocated in this way, the breakdown products of the cells may cause a deleterious effect on healthy cells far removed from the source of the irradiation. The greater the volume of tissue irradiated, the more marked is this constitutional effect of the irradiation. It has been shown experimentally that if one lymph gland is shielded completely from radiation and the rest of the body is irradiated, the shielded gland is still affected.[46] In fact, a lymph node exposed to several thousand r shows very little more damage than that seen in a comparable gland that had been shielded from direct radiation, while the rest of the body had received only a few hundred r. Such effects are sometimes called the "constitutional" effects of radiation. However other names are also used for such a response. One such name has been "radiation shock" and when the symptoms are milder the term "radiation sickness" is used.

Characteristically, when an animal has been irradiated there may be no observable effect for some length of time. Then there is a distinct response that involves lowering of the body temperature, lowering of blood pressure, escape of fluids from the circulatory system, changes in chemical composition of the plasma and changes in nervous system activity.[22,27,30]

The constitutional aspect of radiation sickness seems to arise from the release of large amounts of cell breakdown products into the circulatory system. The normal defense mechanisms of the body cannot handle such a large amount of the toxic products, particularly those from the cell nucleus, and all organ systems of the body are then affected. The response of different individuals does not follow a consistent pattern.[71] One person suffering from radiation sickness may show nervous involvement, another respiratory involvement, a third involvement of the urinary tract and so forth. Usually the symptoms of the digestive tract

predominate and hence radiation sickness is almost always accompanied by vomiting.

General Remarks about Blood

The blood is a labile tissue and as such represents a rather characteristic system. In this labile tissue the component cells are relatively independent of one another and are capable of moving some distance from their point of origin. While there are several types of cells in the blood, there does seem to be one point in common and that is that the cells seem to be discharging their function only when the blood is in motion.

Blood cells, like other cells of the body, arise in a germinal layer and following development, move away from that layer. In the case of the blood the cells move into the general circulation where their life span is spent. Different types of cells have different life spans and for each cell type, as the old cells die, they are replaced by new cells from the germinal layer at a rate that keeps a relatively constant number of each type of cell in the circulation. This in effect is a series of simultaneous feedback systems.

Blood, like other tissues, has cells in the resting state, in the mitotic state, in the differentiating state and in process of degeneration. In other tissues cells in all stages of the life cycle are generally found close together or even intermixed. In blood, however, once the cells have differentiated or matured they move some distance from their point of formation so one finds cells in the resting stage and in the mitotic stage in the germinal layers while the mature cells and the degenerating or dying cells are removed from the germinal layers.

Blood serves at least two principle functions. First it carries food and fluid from the digestive tract to all other parts of the body. Second, it carries oxygen from the lungs to all parts of the body and carbon dioxide from all parts of the body back to the lungs. Of these processes the oxygen turnover represents the most rapid process. The importance of this rapid turnover can best be illustrated by the speed with which oxygen starvation leads to a lethal effect. Roughly speaking, a man can exist 8 weeks without food, 8 days without water, but less than 8 min without oxygen. This high rate of turnover is facilitated by the fact that a typical blood cell completes the lung circulation (heart through lungs back to heart) in about 10 sec.

Blood is essentially a series of specialized cells moving in a fluid matrix. The composition of this matrix varies from time to time and place to place according to the condition of the organ that it traverses. The organs in turn respond to minute changes in composition of the fluid and are capable of adding or subtracting constituents according to the local requirements. The changes in chemical composition that may occur may be of primary importance to the organ system but undetectable in the composition of the blood. For this reason the blood may be considered as a fluid of constant composition and quality.

This constancy of composition applies only to the fluid component of the blood, however. The cellular composition of the blood depends upon altitude, general state of health, activity, time of day, and numerous other factors. Despite this if the blood count of a generally healthy individual is considered at the same time of day on different days under conditions where all other parameters are held constant, the results are found to be constant. No two individuals are exactly the same, but each individual is constant.

Types of Blood Cells

Peripheral blood of humans contains three principle types of blood cells.

(1) Red blood cells. These cells in the human have no nucleus and therefore cannot divide. They function entirely within the circulatory system carrying both oxygen and carbon dioxide and die without ever leaving the circulatory system.

(2) White blood cells. There are at least three different kinds of white cells. The lymphocytes have a clear cytoplasm and a con-

densed nucleus. Cells with a granular cytoplasm are called either leucocytes or granulocytes. These cells have a lobed nucleus that changes shape with increasing age. As the cell ages, the number of lobes on the nucleus increases. The third type of white cell is the monocyte and is found only in very low numbers under normal conditions.

(3) Platelets. These cells appear to be cytoplasmic fragments of a "giant" cell in the germinal layers. These cells are thought to be involved in the process of blood clotting.

The total number of blood cells in a human is very large. On the average there are 5 million red blood cells per cubic millimeter of blood for a man (women have slightly less). If there are then 5 million cubic millimeters of blood there would be 25 x 10^{12} non-nucleated cells in suspension. There are 1 or 2 white cells for each 100 red cells so the total number of cells is of a high order of magnitude. These cells make a complete trip of the circulatory system in about 2 min.

The germinal layer for blood cells is located in a variety of areas. The cells arise from a spongy tissue distributed throughout the bone marrow, in the spleen, the lymph glands and scattered lymphoid tissue lying along the intestinal canal and elsewhere. This spongy tissue consists of a supporting framework containing a large number of embryonic "reticulum" cells.

Development of Blood Cells

The reticulum cells from which the blood cells are formed can give rise to several different types of mature blood cells and can do so at a very high rate. When the mature cells are formed they are stored for later release. The storage is accomplished within spongy tissue in which newly formed cells are held in clumps. In normal states of health, the blood cells are released at a rate that just balances the loss of cells arising from cell death.

The red cell develops from the reticulum cell of the bone marrow through a rather complex pattern in which hemoglobin is deposited in the cell and the nucleus of the cell is lost. At one stage in the development the red cell contains both hemoglobin and a nucleus. These nucleated red cells are susceptible to radiation and actually disappear from the bone marrow within 24 hr of post-irradiation.[94] Regeneration begins about 7 days after post-irradiation. When mature red cells are released into the circulation they exist for 110-120 days on the average. Death of the cell occurs either by dissolution in the spleen or in the general circulation.

Another type of cell also originates from the reticulum cells of the bone marrow. These are the granulocytes.

$$\text{myeloblasts} \rightarrow \text{myelocytes} \begin{cases} \rightarrow \text{neutrophils} \\ \rightarrow \text{eosinophils} \\ \rightarrow \text{basophils} \end{cases}$$

The three types of granulocytes that result are distinguishable on the basis of their response to different stains. The granules in the cytoplasm of the most numerous of the cells respond to neutral stains and the cells are called neutrophils. The next most numerous cells have granules that are stained by acid stains and these cells are called eosinophils. The least numerous of the granulocytes are those cells whose granules are stained by basic stains and they are called basophils. When the granulocytes are mature they are released into the circulation and have a life span of about three days.

The reticulum cells that give rise to the lymphocytes are spread throughout the body in the lymph nodes and the lymph tissue. The lymphocytes can be produced in very large number if needed, however, they have a very short life span. Individual lymphocytes live in the circulatory system for less than one day. The cells terminate their existence by passing into the digestive tract and there die and break up.

Irradiation of Blood

It should be evident from the space occupied by the circulatory system that mature blood cells will be involved in whatever part of the body is

exposed to irradiation. However, with care and the use of localized fields, it is generally possible to avoid irradiating the blood-forming organs unless such action is desired. It is difficult, however, to avoid irradiation of lymph glands where lymphocytes are formed.

Observations have been made to study the effect of irradiation of various parts of the human body on circulating leukocytes and lymphocytes. It was found that the most pronounced effect on leukocytes and lymphocytes was observed after irradiation of the abdomen, followed in order by the thorax, neck, skull and limbs. After irradiation the cell count tends to return to normal.[45] This would suggest that lymphopenia following irradiation is due to destruction of lymphocyte-forming tissue in the field of irradiation and return to normalcy is accomplished by increased activity of the remaining lymphocyte forming tissue in an effort to maintain a constant level of lymphocytes in the blood.

The typical response of the blood-forming organs to irradiation is the reduction in the number of all types of circulating cells. The time of response of the cells is different for each type. The maximum reduction in the red blood cells occurs some weeks after irradiation. However, there is an increase in the fragility of these cells before the number is reduced.[5] With granulocytes the maximum reduction is in terms of days while with lymphocytes the fall in count is reflected in hours. This time relation correlates well with the life span of the different cells.[22,27,47] The cell with the shortest life span (lymphocyte) is the first to show diminution in number, while that with the longest existence (the red blood cells) takes the longest to show the reduction. The effect observed cannot be explained by an action of radiation on mature cells in the circulation since they are resistant to the radiation. It is apparently due to the action of radiation in cutting off the supply of new cells by preventing mitosis in the blood-forming tissues.

If this view is correct, it then appears that radiation blocks the formation of all new blood cells by interfering with mitosis at the level of the germinal layer. The cells that are in circulation die off at their regular rate, but since they are not replaced the net result is a decrease in number in the peripheral blood. By this view, the results observed in a blood count following exposure to radiation would depend upon the time past irradiation that the count was made and how this time was related to the life span of the different cells.

When low doses of radiation are used, the decrease in cell number is temporary. Lymphocyte counts vary rapidly and over a considerable range for even small doses of radiation. Because of this it is difficult to use this count as a criterion of radiation damage.

Neutrophil counts are often used as a criterion of the amount of exposure to radiation and they seem to offer a reliable index. The decrease observed with neutrophils is neither as sudden nor as extreme as is the change of lymphocytes. In addition to the use of neutrophil counts, examination of the neutrophil cells offers an index of radiation exposure. Normal neutrophil cells have neuclei with 4 to 5 lobes. Recovery of the neutrophil count following exposure to radiation involves release of younger cells from the germinal layers and these younger cells have fewer lobes. Hence the average number of lobes per nuclei may be reduced to 2 or 3 following irradiation.[68]

Reduction in the number of red cells following exposure to radiation occurs much later than does the reduction of other cell types. However, because of limited recovery power, damage to the germinal layers that give rise to red cells may be more serious than it is with the other cell types.

In general one may say that the blood picture seen after radiation exposure therefore varies with the total amount of blood-forming tissue irradiated, the length of time between exposures and blood examination and the degree of recovery that has occurred. With so many variables it is no wonder that many inconsistent accounts by different authors have arisen.

Irradiation Effects on the Blood of Humans. Cell disturbances in the blood of humans following irradiation have been investigated under a great many conditions, but perhaps the most dramatic is the case where humans have been exposed to atomic blasts. (Nagasaki and Hiroshima.) The Atomic Bomb Casualty Commission has conducted surveys of the survivors each year since the atomic bombs were exploded.[51,52,60] In this survey one of the factors considered in detail is the observable changes in the peripheral blood cellular components. Each commission report has found a number of cases of leukemia. In each survey it is found that there is a much higher incidence of leukemia in groups closer to the radiation center. Chronic myelogenous leukemia was the most frequent type, acute myelogenous leukemia was second in frequency. There was only one case of chronic lymphatic leukemia observed, but this is an exceptionally rare disease in the Japanese. In the largest number of cases the onset of leukemia is about five years after exposture. In addition to the leukemia there have also been reported a number of cases of refractory anemia where leukemia was not present. Again the fatal symptoms of this disease in which there is a deficiency of hemoglobin occurs some four to seven years after exposure.

The cause of leukemia is still an enigma. It would appear to involve (1) hereditary capacity for abnormal growth and (2) various physical, chemical or metabolic agents capable of precipitating the disease. These factors would seem to involve direct injury to the genetic factors of man by the radiation so that pronounced effects would be expected in future generations.[60]

It is perhaps interesting that somewhat the same picture as above has been reported under less severe circumstances where radiation has been used clinically. Of seven cases reported where x-rays were used for therapy on alkylosing spondylitis five patients developed myeloid leukemia and two aplastic anemia even though only one patient was to be considered as having received excess x-ray dosage.[20]

The Role of Hormones. The action of numerous compounds, both natural and unnatural, can be explained on the basis of action of those compounds at the level of the blood-forming organ. For example, the endocrine organs affect sensitivity to radiation.

This will be discussed in some detail when the reproductive system is considered. However, other endocrine organs such as the adrenals and the thyroid also have a role to play. Removal of the adrenals increases the sensitivity of the animal to irradiation.[88] This effect is reversed if one then injects whole adrenal extract.[52] The hormones in the adrenal extract hasten recovery of the bone marrow from the damage done by the irradiation. If cortisone (an adrenal hormone) is administered to a normal animal, that animal becomes more sensitive to total body irradiation, and less able to combat the bacterial or viral infections that may accompany irradiation. If the thyroid gland is removed the radiosensitvity of the skin is reduced.[14] Conversely, if thyroid hormone is administered in excess the skin becomes more susceptible to total body irradiation. The effect of the thyroid hormone is apparently related to the fact that the hormone increases the rate of metabolism which in turn affects the capillary circulation of the blood. Further, however, the increased metabolic rate affects the rate of activity of the lymphatic tissue and in this way interacts with the effects of irradiation.

Repeated or Excessive Irradiation. If the same germinative area of the blood system is irradiated repetitiously, the ability of the blood cells to differentiate may be lost before proliferation is checked and a gross overproduction of one of the types of blood cells may result. These cells will be poured into the blood stream as abnormal cells. They may either be abnoral in appearance or they may still be capable of cell division. These cells then cause a gross interference with the normal functioning of the blood and this results in a detrimental condition to all the organs of the body.[89]

If excessive doses of radiation are given there results a permanent depression of all cell divi-

sion in the blood-forming tissues. Irradiation of even a selected area of the body, if overdone, upsets the delicate normal balance between cell production and cell death. As a result the germinal areas outside of the irradiated area must contribute to maintaining the balance. If the area of irradiation is large the surviving germinal areas may not be able to meet the new demands and the entire feed-back system breaks down.

Normal Process of Blood Clotting

So far we have discussed only the cell constituents of blood. Actually, only one-half of the weight of the blood is due to the cellular component. The remainder of the blood is a fluid called plasma that contains proteins, fats, and a considerable number of inorganic ions in varying amounts.

With the proper precautions, blood may be separated *in vitro* into the cellular components and a clear yellow plasma. This plasma is the same fluid that passes through the capillary walls to bath the cells in an intact animal.

Blood, withdrawn from a living body, clots at room temperature in a few minutes. The general mechanism of this clotting action has been understood for a number of years. There are still many refinements and details not understood in the problem of blood clotting but these refinements are not necessary to our understanding of the action of radiation and hence will not be considered here.

All components necessary for the clotting of blood are present at all times in the bloodstream and are present in a fluid or nonclotted form. When blood is exposed to the air whether through a cut or lesion or in a test tube, the following reactions are thought to take place:

Prothrombin (A protein in blood)	Thromboplastin (from platelets) $\xrightarrow[Ca^{++}]{}$	Thrombin (A modified protein)
Fibrinogen (A soluble protein of blood)	Thrombin $\longrightarrow$	Fibrin (An insoluble protein)

The prothrombin molecule is a protein formed in the liver and carried in the blood stream. When it is in the form found normally in the blood the protein is inactive. When injury occurs that in some way damages the platelets or when the blood vessels' walls are ruptured and tissue juices come into contact with the blood, a substance called thromboplastin is released and reacts with the prothrombin. In this reaction the prothrombin is converted in the presence of calcium ions to thrombin. The thrombin so formed acts as a catalyst in the conversion of another soluble protein component found in normal blood, namely, fibrinogen, into an insoluble form called fibrin. A clot is formed as a semisolid mass that has the insoluble protein fibrin as a basis and is a dense network of strands that traps the cells and ultimately squeezes out a residual fluid called serum. Blood normally clots in 3-10 min at room temperature. The so-called "coagulation time" is a convenient indication of the speed with which the complicated process of blood clotting occurs in different people. The clotting time is expressed in terms of minutes required for the process to complete to some given endpoints.

Another useful quantitative variable is the viscosity of plasma. The viscosity is measured by the rate at which the blood cells settle or "sink" in an anticoagulant medium. This medium is simply prepared by complexing the calcium in the blood which removes it from its ionic form and thus blocks the coagulation of the blood. The rate of settling is increased in certain physiological and pathological conditions.

Effects of Irradiation on Blood Clotting. The effect of irradiation on coagulation time of the blood is dependent upon the dose of radiation that is absorbed. After small doses the coagulation time may be shortened for a few hours after irradiation. However, when massive doses of radiation are used the coagulation time is prolonged. This change in coagulability of blood has been used as an indicator of an irradiation effect. The platelet count is diminshed

following irradiation and this diminution has been suggested as an index to a safety measure. Under such a system there would be a lower limit permitted for the platelet count. When this lower limit was reached, no further irradiation would be permitted.[89]

When dogs are exposed to 450 r, rabbits to 500-1000 r or guinea pigs to about 200 r, the blood clotting times are lengthened.[91] The prolonged clotting times could be used to explain the presence of skin hemorrhages seen in the animals.[93] In each case the increase in clotting time is accompanied by a decrease in the blood platelets (hence a reduction in thromboplastin). It has also been reported that there is present an anticoagulant factor released into the blood of irradiated animals that would also tend to increase the clotting time of the blood.[3]

Radiation also affects the sedimentation rate of the blood. The effect is to accelerate the rate for a short period of time after exposure which means the blood becomes more fluid through this period of time.

Irradiation of Plasma

Any attempt to understand the effects of radiation on one of the complex systems of the intact animal is complicated by the fact that a healthy animal has remarkable capabilities to adapt to an applied stress. As soon as a stress is applied all the compensatory mechanisms of the body are directed toward readjusting the animal to the normal state. If one investigates the effects of radiation on an animal suffering from some disease state, the problem is even more complex. In this case the defense mechanisms of the body are already under stress attempting to maintain a normal state. If a further insult is applied the breakdown of the control mechanism may occur at some weakened point affected only indirectly by the applied stress. Therefore there may be considerable difficulty in assigning any given result to the action of a stress like irradiation on cells of a particular organ or tissue.

With such complications it is not unreasonable to expect conflicting reports on the action of radiation on systems such as plasma. In fact, one may find reports showing increases, decreases and no effect on the nitrogen level, sugar content and hydrogen ion concentration (acidity) of plasma following irradiation. The results obtained appear to be dependent upon the time interval following irradiation at which samples are obtained and upon the state of recovery of the system when the examination is made.

That there are distinct changes in plasma attributable to radiation effects has been demonstrated clearly in some systems.[89] Experiments using tissue culture techniques have made it clear that irradiation of blood *in vivo* produces changes which are not found when plasma is irradiated outside of the body and free from contact with living cells. Plasma irradiated *in vitro* has no inhibitory effect upon the growth of tissue explants suspended in the culture medium of which it is a constituent part. If, however, the plasma used is derived from a whole animal which has been subjected to total body irradiation, inhibition of growth in the explant is observed.

In short, it appears that there is a definite effect of radiation upon the fluid part of the blood, but the mechanism by which this effect is exerted is not well understood at present.

Skin

It is probably necessary to review some basic concepts concerning the physiology of normal skin before undertaking an understanding of the effect of irradiation.

The skin forms an envelope for the body. There are, in fact, two envelopes. These two envelopes are referred to as the epidermis and the dermis with the two being separated by a basement membrane. The outer envelope is the epidermis and it does not contain blood vessels. In spite of this, however, the epidermis is not a dry tissue. The cells (except for the outermost layers) are bathed in a moist medium that is derived from the blood and drained back into circulation by means of the lymph vessels. The condition of the cells in this outer envelope is in some respects similar to those which are obtained in tissue culture. The epidermal cells

consist of an orderly arrangement of cells which are derived from a "germinal" or basal layer which in turn rests on the basement membrane. All the cells of the basal layer have the capacity of cell division and at any given time there are many mitotic figures present among the resting cells. The cells of the outer layers of the epidermis do not divide but show progressive increase in differentiation as they approach the surface of the body. Cells from the basal layer travel slowly outward toward the surface of the body and change slowly as they move. When one of the differentiated cells die, it is replaced by another ultimately derived from the germinal layer.

This process of cell division and cell differentiation in the skin goes on all through life. Normal skin is essentially a feed-back mechanism by which the activity of the germinal layer is kept in step with that of the other layers of the skin. The balance is maintained by the fact that some daughter cells remain in the germinal layer as potentially dividing cells instead of differentiating. Each daughter cell formed has within itself the ability to undergo subsequent division or to differentiate. It should be apparent that one daughter cell remains in the germinal layer for each cell which migrates away from the basement membrance to the more superficial layers of the skin. Hence, there is always the same number of cells in the germinal layer.

The differentiated cells that form the outer layer eventually become a dead, dry, "keratin" which will eventually rub off. This keratin surface is what provides the insulating and weatherproofing characteristics of the skin. In most places on the body this outer layer is about 1 mm thick, but in selected areas such as the sole of the foot, the thickness may be several millimeters.

The basement membrane upon which the epidermis rests has a structure analagous to that seen in corrugated cardboard. The net effect of the undulations of the layer is to increase the total area and hence give an extended surface for the germinal layer of cells. In addition to this undulated structure, the presence of pockets in the form of hair follicles and modified sweat glands also add to the total area available for the germinal layer.

In the deeper layers of the epidermis are cells that upon exposure to sunlight form a pigment.[6] The mechanism by which the pigment is formed is not understood. One thing seems clear; namely, in white races the pigmentation is seasonal and varies with the amount of sunlight. If the pigmentation is irregular, one recognizes the result as freckles.

The dermis or that part of the skin lying under the basement membrane has a very different structure than does the epidermis. The dermis is essentially "packing material"[89] which also acts as a heat insulator. It is composed of connective tissue, elastic fibers and fat. The connective tissue is made up of fine fibrils between which droplets of water are stored. It is this water that gives a certain elasticity to the skin.

The dermis varies greatly in thickness over the area of the body. In the connective tissue part of the dermis one finds blood vessels, nerves, and nerve endings, particularly those associated with the sense of touch. The part of the dermis nearest to the epidermis contains a fine capillary bed.

The dermis, because of its water content, fiber content and fat gives the resilience that one finds in the skin. Like the epidermal cells, dermal cells also may contain pigments. However, the pigmentation observed in this layer is permanent and will not wear off.

Irradiation of the Skin

The skin is a very highly specialized organ system that discharges many function besides simply covering the outer surface of the body. The skin is easily injured but at the same time has a remarkable power of repair. Fortunately, most injuries that occur to the skin involve a relatively small percentage of the total area of the body. Because of this there is generally plenty of normal tissue that remains and the healing process can then begin from this tissue.

If injury covers a wide area of the body surface all at once, the consequences can be serious simply because there is not sufficient normal skin left to dominate the repair process.

The "skin tolerance" to radiation has been one of the limiting factors in radiotherapeutic technique no matter what equipment is used. This tolerance has been very useful in checking gross overdosage in radiation therapy because any tendency toward overdosage is followed very soon by visible evidence of a mistake. The skin effect is, however, less evident as the wavelength of the radiation is shortened.[76] In this way the highly penetrating radiations of many modern high energy units pass through the skin with little effect on it. Some high energy machines deliver a dose which actually "builds up" to a maximum value with increase in depth of penetration. The tissue immediately below the skin actually receives a dose of radiation which is greater than that received by the skin because of scattering within the tissue layers.

When the epidermis is injured by radiation or by other means, the injured or lost tissue is replaced by an overgrowth of the adjacent non-injured tissue cells. When the dermis is injured there is a more complex process of recovery although the same general mechanism seems to hold. The different types of cells found in the dermal layer all have their own characteristic powers of recovery. The connective tissue cells repair most rapidly. Therefore after severe damage whether caused by an acute injury or a series of small injuries spread over an extended period of time, the connective tissue cells "out repair" the other tissues and scar tissue is formed. This scar tissue is, of course, totally different from normal skin and cannot carry out the normal functions observed in skin. Once the scar tissue is formed it is permanent and the skin of that area never does recover its normal function.

Agents such as sunlight may be beneficial to the skin in small amounts but becomes injurious when received in excess. Excessive amounts of sunlight may give rise to a condition known variously as seaman's skin, farmer's skin, or tropical skin. This condition is essentially the production of lesions by radiation. In the skin grossly over-exposed to the sun the injury may go even further and the functioning of skin cells become so disorganized that permanent changes may occur which may lead to cancer.[89] Though this is a possible action, formation of cancer by this method is improbable or rare in temperate climates. Even in areas where such events can occur it takes a very long time to produce. For example, it takes about four years of haphazard exposure to x-ray to produce cancer as compared with a period of about 40 years to produce a sun cancer.

Production of Erythema. As soon as the early workers in the field realized that it was penetrating radiation that actually caused injury to the skin, the reactions of the skin to planned radiation dosage under a great many physical parameters were studied. It was found that radiation would produce a definite reddening of erythema of the skin; this effect was transient and disappeared without leaving any recognizable effect.

There are numerous detailed descriptions of the erythema caused by x-ray[54,80,81] or by beta particles.[50,99] It will suffice here to simply summarize a number of statements that appear to apply equally well to the response to either type of radiation.

The production of this erythema is influenced by many factors. Some of these factors are physical and some are biological. Among the physical factors are wavelength of the radiation, duration of irradiation, whether the radiation is given in single or multiple exposures, and the intervals between irradiation.

By adjustment of the physical factors it is possible to divide the dose, reduce the radiation intensity and in this way increase the total dose of radiation administered without increasing the amount of damage. By this technique it is possible to increase the radiation dose by a factor of 20 times without causing damage to the skin.[92] Obviously there is a limit to this.

Biological factors also influence the production of erythema by irradiation. Such factors as

sex, skin site chosen, race, age, degree of tanning, color of the skin and the inclusion of bone all modify the erythema response.

Production of erythema by irradiation is a convenient biological indicator of dosage providing all the physical factors are controlled and only one individual assesses what is a proper erythema. A standard form is generally followed so that the skin erythema dose is considered as that irradiation that will just produce a slight reddening or tinting of the skin in 80 percent of persons exposed.[80]

The reaction observed following the skin erythema dose is actually the second step of a three phase reaction.[54] The entire reaction consists of first a reddening which develops within a few hours or up to three days after exposure and then disappears. This early erythema is not produced in humans by doses below 300 r.[38] Between 300 and 600 r the color intensity of the reaction is independent of dose but rather is determined mainly by the color and texture of the skin of the person irradiated. The second step or phase is a reddening that develops from 10 to 28 days after exposure. The color in this phase deepens then fades. It is this stage which is the real erythema dose. As the reddening fades it may be followed by an increase in pigmentation that appears as enormous freckles. These freckles may be permanent. In the skin of colored races this freckle formation is replaced by a redistribution of the pigment already present. The mechanism for this pigment effect is not at present understood but the area involved seems to be more sensitive than normal to further irradiation.

The third stage of the reaction is a reddening that develops about the sixth week after exposure. This stage appears in a proportion of the cases but not in all. The erythema of this stage is like that of the first stage in that the reddening is independent of the dose over a wide range.

The severity of the reaction of the skin to irradiation depends upon the conditions under which the radiation is given. Very low doses produce no detectible alteration in the skin. When an effective dose is reached there may be nothing more than a temporary flush of the skin. As the dosage is increased, the first inevitable change that occurs is that the hair of the irradiated person loosens in the irradiated area. This stage is followed by actual loss of the hair from their follicles.[8] This is a temporary condition and the hair regrows within three or four months.

Radiation stops the growth of hair by its action on the dividing cells lining the hair follicles. When the cell division stops, the hair loosens and falls out. This is followed by a rapid regeneration but the timing of both the epilation and repair is influenced by the particular state of hair development at the time of irradiation.[89] The replacement hair may have different characteristics (including color) than did the hair present before irradiation.[8,67] It is possible, of course, that the dividing cells of the hair follicle can be killed by excessive irradiation. If this happens the hair does not return but the entire area is permanently denuded.[92]

A somewhat different mechanism seems to be operating in the case of thindown hits from heavy nuclei cosmic radiation. In this case the irradiation can cause the hair follicle to produce a white hair instead of a colored one. After some time the hair falls out and does not return, in contrast to the action of x-ray.[16] The phenomenon involving cosmic radiation is not sufficiently well understood to permit explanation at present.

At doses slightly greater than the epilation dose of x-ray, erythema is produced in the majority of individuals. This generally occurs at about 1000 r for gamma rays and about 400 r for soft x-ray.[38] If the dose level is increased still further the erythema may take the form of a dark red or purple reaction in the skin. This is followed by the formation of blisters, small at first but then increasing in size by the coalescing of different lesions. The blisters are formed in the epidermis as a result of cell destruction which allows fluid to collect between the cell layers. With the collection of fluid, tension on the skin develops and this

tension means the blisters will break easily. This leaves the basal layer or even the dermis of the skin exposed and this raw surface appears red or bright pink oozing a clear yellow fluid.[80]

After very heavy irradiation a lethal effect may be produced on a wide scale including both the epidermis and dermis. This condition gives rise to a radiation ulcer or burn.[55] During such an exposure the radiation behaves without discrimination by destroying cells independent of their state at the time of exposure.

Irradiation and Thermal Burns. The action of radiation at the level of the skin is somewhat analogous to the action seen in thermal burns.[4] Because of the similarity some work has been done to assist in understanding the interrelationship between thermal burns and irradiation injury as a result of nuclear explosions or exposure. Animals subjected to only thermal burns either die within 48 hours or else they recover. This action permits one to calculate a median lethal burn area (LA) expressed as a percentage of the total body surface area. Using this nomenclature an LA-50 (48 hr) dose for thermal burn alone is 33 percent. If 100 r of total body irradiation is used in conjunction with the thermal burn, the LA-50 dose for the thermal burn is reduced to 30 percent. 250 r reduce the LA-50 to 27 percent, while 500 r reduce it to 24 percent. Radiation doses of 100 r to 250 r have no lethal effects in and of themselves for the rats used in such experiments. These experiments may be viewed in a slightly different way for the sake of clarification. Burns covering 30 to 35 percent of the animal body caused death in 50 percent of the control animals. If 100 r of x-ray are given at the same time there is 65 percent mortality and if 250 r of x-ray are given with 31-35 percent thermal burns, there is a 100 percent mortality of the animals. This is of considerable interest since mortality from the burns alone occurs during the "shock phase" (within 49 hr) which is a period of time too short for the effects of irradiation to be seen. Careful graduation of doses in such studies has led to the concept that there is an increased fragility of the red blood cells which results in an increased loss of these red cells. This factor may be important in the elevated death rate of the irradiated-burned animals. Hence, while there may be a superficial similarity in radiation and thermal burns, there are also complicating differences.

Beta Ray Burns. Some experience with beta ray burns has been gained through studies of accidental exposure.[50] Beta ray burns offer an odd combination of both thermal type and x-ray type burns. If one considers beta rays of 1 mev maximum energy, about 90 percent of the radiation is absorbed in the first 3 mm of tissue and 99 percent is absorbed in the first 6 mm of tissue. In the accidental exposures studied the total dosage was from 3000 to 16,000 rep. This would mean that the dosage at 3 mm depth would be 300-1600 rep and at 6 mm depth, 30-160 rep. With this dosage the skin reaction falls into four distinct phases: (1) Initial erythema and edema occurs with some blanching in the areas of greatest exposure. This effect reaches a maximum in 48 hr and then subsides. (2) There is a relative absence of signs for 3-5 days. Six to eight days after exposure Phase (3) begins with the development of secondary erythema. For about two weeks the erythema spreads and the number of blisters (vesicles) increase, finally coalescing to form extensive bumps (bullae). Phase (4) is the chronic stage in which some areas with serious vascular damage remain unhealed. At this stage and up to about 12 months time there may be ulcerations and considerable atrophy of soft tissue.

As soon as radiation damage has been done to the skin, cells in the neighborhood begin the process of repair. The success of this repair, of course, depends on the amount of radiation absorbed and the damage done. With slight erythema the repair appears to be complete. With heavier irradiation the repair may not be totally successful and one may have either the deposition of pigment or the formation of scar tissue. There may also be over-compensation on the part of connective tissue so that locally, the amount of tissue finally present is in excess of

consist of an orderly arrangement of cells which are derived from a "germinal" or basal layer which in turn rests on the basement membrane. All the cells of the basal layer have the capacity of cell division and at any given time there are many mitotic figures present among the resting cells. The cells of the outer layers of the epidermis do not divide but show progressive increase in differentiation as they approach the surface of the body. Cells from the basal layer travel slowly outward toward the surface of the body and change slowly as they move. When one of the differentiated cells die, it is replaced by another ultimately derived from the germinal layer.

This process of cell division and cell differentiation in the skin goes on all through life. Normal skin is essentially a feed-back mechanism by which the activity of the germinal layer is kept in step with that of the other layers of the skin. The balance is maintained by the fact that some daughter cells remain in the germinal layer as potentially dividing cells instead of differentiating. Each daughter cell formed has within itself the ability to undergo subsequent division or to differentiate. It should be apparent that one daughter cell remains in the germinal layer for each cell which migrates away from the basement membrance to the more superficial layers of the skin. Hence, there is always the same number of cells in the germinal layer.

The differentiated cells that form the outer layer eventually become a dead, dry, "keratin" which will eventually rub off. This keratin surface is what provides the insulating and weatherproofing characteristics of the skin. In most places on the body this outer layer is about 1 mm thick, but in selected areas such as the sole of the foot, the thickness may be several millimeters.

The basement membrane upon which the epidermis rests has a structure analagous to that seen in corrugated cardboard. The net effect of the undulations of the layer is to increase the total area and hence give an extended surface for the germinal layer of cells. In addition to this undulated structure, the presence of pockets in the form of hair follicles and modified sweat glands also add to the total area available for the germinal layer.

In the deeper layers of the epidermis are cells that upon exposure to sunlight form a pigment.[6] The mechanism by which the pigment is formed is not understood. One thing seems clear; namely, in white races the pigmentation is seasonal and varies with the amount of sunlight. If the pigmentation is irregular, one recognizes the result as freckles.

The dermis or that part of the skin lying under the basement membrane has a very different structure than does the epidermis. The dermis is essentially "packing material"[89] which also acts as a heat insulator. It is composed of connective tissue, elastic fibers and fat. The connective tissue is made up of fine fibrils between which droplets of water are stored. It is this water that gives a certain elasticity to the skin.

The dermis varies greatly in thickness over the area of the body. In the connective tissue part of the dermis one finds blood vessels, nerves, and nerve endings, particularly those associated with the sense of touch. The part of the dermis nearest to the epidermis contains a fine capillary bed.

The dermis, because of its water content, fiber content and fat gives the resilience that one finds in the skin. Like the epidermal cells, dermal cells also may contain pigments. However, the pigmentation observed in this layer is permanent and will not wear off.

Irradiation of the Skin

The skin is a very highly specialized organ system that discharges many function besides simply covering the outer surface of the body. The skin is easily injured but at the same time has a remarkable power of repair. Fortunately, most injuries that occur to the skin involve a relatively small percentage of the total area of the body. Because of this there is generally plenty of normal tissue that remains and the healing process can then begin from this tissue.

If injury covers a wide area of the body surface all at once, the consequences can be serious simply because there is not sufficient normal skin left to dominate the repair process.

The "skin tolerance" to radiation has been one of the limiting factors in radiotherapeutic technique no matter what equipment is used. This tolerance has been very useful in checking gross overdosage in radiation therapy because any tendency toward overdosage is followed very soon by visible evidence of a mistake. The skin effect is, however, less evident as the wavelength of the radiation is shortened.[76] In this way the highly penetrating radiations of many modern high energy units pass through the skin with little effect on it. Some high energy machines deliver a dose which actually "builds up" to a maximum value with increase in depth of penetration. The tissue immediately below the skin actually receives a dose of radiation which is greater than that received by the skin because of scattering within the tissue layers.

When the epidermis is injured by radiation or by other means, the injured or lost tissue is replaced by an overgrowth of the adjacent non-injured tissue cells. When the dermis is injured there is a more complex process of recovery although the same general mechanism seems to hold. The different types of cells found in the dermal layer all have their own characteristic powers of recovery. The connective tissue cells repair most rapidly. Therefore after severe damage whether caused by an acute injury or a series of small injuries spread over an extended period of time, the connective tissue cells "out repair" the other tissues and scar tissue is formed. This scar tissue is, of course, totally different from normal skin and cannot carry out the normal functions observed in skin. Once the scar tissue is formed it is permanent and the skin of that area never does recover its normal function.

Agents such as sunlight may be beneficial to the skin in small amounts but becomes injurious when received in excess. Excessive amounts of sunlight may give rise to a condition known variously as seaman's skin, farmer's skin, or tropical skin. This condition is essentially the production of lesions by radiation. In the skin grossly over-exposed to the sun the injury may go even further and the functioning of skin cells become so disorganized that permanent changes may occur which may lead to cancer.[89] Though this is a possible action, formation of cancer by this method is improbable or rare in temperate climates. Even in areas where such events can occur it takes a very long time to produce. For example, it takes about four years of haphazard exposure to x-ray to produce cancer as compared with a period of about 40 years to produce a sun cancer.

Production of Erythema. As soon as the early workers in the field realized that it was penetrating radiation that actually caused injury to the skin, the reactions of the skin to planned radiation dosage under a great many physical parameters were studied. It was found that radiation would produce a definite reddening of erythema of the skin; this effect was transient and disappeared without leaving any recognizable effect.

There are numerous detailed descriptions of the erythema caused by x-ray[54,80,81] or by beta particles.[50,99] It will suffice here to simply summarize a number of statements that appear to apply equally well to the response to either type of radiation.

The production of this erythema is influenced by many factors. Some of these factors are physical and some are biological. Among the physical factors are wavelength of the radiation, duration of irradiation, whether the radiation is given in single or multiple exposures, and the intervals between irradiation.

By adjustment of the physical factors it is possible to divide the dose, reduce the radiation intensity and in this way increase the total dose of radiation administered without increasing the amount of damage. By this technique it is possible to increase the radiation dose by a factor of 20 times without causing damage to the skin.[92] Obviously there is a limit to this.

Biological factors also influence the production of erythema by irradiation. Such factors as

sex, skin site chosen, race, age, degree of tanning, color of the skin and the inclusion of bone all modify the erythema response.

Production of erythema by irradiation is a convenient biological indicator of dosage providing all the physical factors are controlled and only one individual assesses what is a proper erythema. A standard form is generally followed so that the skin erythema dose is considered as that irradiation that will just produce a slight reddening or tinting of the skin in 80 percent of persons exposed.[80]

The reaction observed following the skin erythema dose is actually the second step of a three phase reaction.[54] The entire reaction consists of first a reddening which develops within a few hours or up to three days after exposure and then disappears. This early erythema is not produced in humans by doses below 300 r.[38] Between 300 and 600 r the color intensity of the reaction is independent of dose but rather is determined mainly by the color and texture of the skin of the person irradiated. The second step or phase is a reddening that develops from 10 to 28 days after exposure. The color in this phase deepens then fades. It is this stage which is the real erythema dose. As the reddening fades it may be followed by an increase in pigmentation that appears as enormous freckles. These freckles may be permanent. In the skin of colored races this freckle formation is replaced by a redistribution of the pigment already present. The mechanism for this pigment effect is not at present understood but the area involved seems to be more sensitive than normal to further irradiation.

The third stage of the reaction is a reddening that develops about the sixth week after exposure. This stage appears in a proportion of the cases but not in all. The erythema of this stage is like that of the first stage in that the reddening is independent of the dose over a wide range.

The severity of the reaction of the skin to irradiation depends upon the conditions under which the radiation is given. Very low doses produce no detectible alteration in the skin. When an effective dose is reached there may be nothing more than a temporary flush of the skin. As the dosage is increased, the first inevitable change that occurs is that the hair of the irradiated person loosens in the irradiated area. This stage is followed by actual loss of the hair from their follicles.[8] This is a temporary condition and the hair regrows within three or four months.

Radiation stops the growth of hair by its action on the dividing cells lining the hair follicles. When the cell division stops, the hair loosens and falls out. This is followed by a rapid regeneration but the timing of both the epilation and repair is influenced by the particular state of hair development at the time of irradiation.[89] The replacement hair may have different characteristics (including color) than did the hair present before irradiation.[8,67] It is possible, of course, that the dividing cells of the hair follicle can be killed by excessive irradiation. If this happens the hair does not return but the entire area is permanently denuded.[92]

A somewhat different mechanism seems to be operating in the case of thindown hits from heavy nuclei cosmic radiation. In this case the irradiation can cause the hair follicle to produce a white hair instead of a colored one. After some time the hair falls out and does not return, in contrast to the action of x-ray.[16] The phenomenon involving cosmic radiation is not sufficiently well understood to permit explanation at present.

At doses slightly greater than the epilation dose of x-ray, erythema is produced in the majority of individuals. This generally occurs at about 1000 r for gamma rays and about 400 r for soft x-ray.[38] If the dose level is increased still further the erythema may take the form of a dark red or purple reaction in the skin. This is followed by the formation of blisters, small at first but then increasing in size by the coalescing of different lesions. The blisters are formed in the epidermis as a result of cell destruction which allows fluid to collect between the cell layers. With the collection of fluid, tension on the skin develops and this

tension means the blisters will break easily. This leaves the basal layer or even the dermis of the skin exposed and this raw surface appears red or bright pink oozing a clear yellow fluid.[89]

After very heavy irradiation a lethal effect may be produced on a wide scale including both the epidermis and dermis. This condition gives rise to a radiation ulcer or burn.[55] During such an exposure the radiation behaves without discrimination by destroying cells independent of their state at the time of exposure.

Irradiation and Thermal Burns. The action of radiation at the level of the skin is somewhat analogous to the action seen in thermal burns.[4] Because of the similarity some work has been done to assist in understanding the interrelationship between thermal burns and irradiation injury as a result of nuclear explosions or exposure. Animals subjected to only thermal burns either die within 48 hours or else they recover. This action permits one to calculate a median lethal burn area (LA) expressed as a percentage of the total body surface area. Using this nomenclature an LA-50 (48 hr) dose for thermal burn alone is 33 percent. If 100 r of total body irradiation is used in conjunction with the thermal burn, the LA-50 dose for the thermal burn is reduced to 30 percent. 250 r reduce the LA-50 to 27 percent, while 500 r reduce it to 24 percent. Radiation doses of 100 r to 250 r have no lethal effects in and of themselves for the rats used in such experiments. These experiments may be viewed in a slightly different way for the sake of clarification. Burns covering 30 to 35 percent of the animal body caused death in 50 percent of the control animals. If 100 r of x-ray are given at the same time there is 65 percent mortality and if 250 r of x-ray are given with 31-35 percent thermal burns, there is a 100 percent mortality of the animals. This is of considerable interest since mortality from the burns alone occurs during the "shock phase" (within 49 hr) which is a period of time too short for the effects of irradiation to be seen. Careful graduation of doses in such studies has led to the concept that there is an increased fragility of the red blood cells which results in an increased loss of these red cells. This factor may be important in the elevated death rate of the irradiated-burned animals. Hence, while there may be a superficial similarity in radiation and thermal burns, there are also complicating differences.

Beta Ray Burns. Some experience with beta ray burns has been gained through studies of accidental exposure.[50] Beta ray burns offer an odd combination of both thermal type and x-ray type burns. If one considers beta rays of 1 mev maximum energy, about 90 percent of the radiation is absorbed in the first 3 mm of tissue and 99 percent is absorbed in the first 6 mm of tissue. In the accidental exposures studied the total dosage was from 3000 to 16,000 rep. This would mean that the dosage at 3 mm depth would be 300-1600 rep and at 6 mm depth, 30-160 rep. With this dosage the skin reaction falls into four distinct phases: (1) Initial erythema and edema occurs with some blanching in the areas of greatest exposure. This effect reaches a maximum in 48 hr and then subsides. (2) There is a relative absence of signs for 3-5 days. Six to eight days after exposure Phase (3) begins with the development of secondary erythema. For about two weeks the erythema spreads and the number of blisters (vesicles) increase, finally coalescing to form extensive bumps (bullae). Phase (4) is the chronic stage in which some areas with serious vascular damage remain unhealed. At this stage and up to about 12 months time there may be ulcerations and considerable atrophy of soft tissue.

As soon as radiation damage has been done to the skin, cells in the neighborhood begin the process of repair. The success of this repair, of course, depends on the amount of radiation absorbed and the damage done. With slight erythema the repair appears to be complete. With heavier irradiation the repair may not be totally successful and one may have either the deposition of pigment or the formation of scar tissue. There may also be over-compensation on the part of connective tissue so that locally, the amount of tissue finally present is in excess of

the original. Hence one sees a parallel in the skin responses to x-ray and to beta rays.

Reactions of the skin to radiation all appear to be relatively slow. That is, the observable changes occur only some length of time following irradiation. However, if one does a histological examination of the skin immediately after even small doses of radiation one finds definite alterations.[89] The significance of the histological changes is difficult to assess. This is because it has not been possible to date to relate the changes seen microscopically with the events that at a later date will be observable to the naked eye.

Response of Dermal and Epidermal Layers to Irradiation

We have discussed the general response of the skin to irradiation. It would now seem to be feasible to discuss the effects of irradiation that have been observed on the dermal and epidermal layers specifically.

The germinal layer of cells in the skin, like those in every other tissue possess cells in the resting state, the mitotic state, the differentiating state and the degenerating state. One would expect that these cells would respond to radiation in the same way as any other cell system. Hence, the first action of radiation is to diminish cell division. As in the case of the tissue culture system, the cells affected by radiation may either recover or they may die when division is attempted. Under certain conditions the cells, blocked from further division, may undergo differentiation. If this happens in the epidermal layers of the skin there will be an increased number of keratinized cells at the expense of the other cells in the system. At higher doses of radiation, a predominant number of the germinal layer of cells may be killed. Overproduction of adjacent non-injured cells is then the usual form of repair. The repair may be effected by the formation of a flat sheath of cells that covers the entire area and conserves material. This emergency repair becomes permanent once it has occurred.[13]

Striking changes in the epidermal cells are seen when the cells are exposed at intermittent intervals to small doses of radiation.[89] A complex process is initiated consisting primarily of destruction and secondarily of reparative growth (hyperplasia). Infection is sometimes observed. The changes that occur begin slowly without symptoms but in the course of time the tissue becomes swollen and stiff and hair, if present, is lost. The skin surface is usually dry and may be either smooth and tense from loss of cells or wrinkled and warty from the accumulation of horny differentiated cells. The dryness is due to the effect of irradiation on the secreting cells of the glands lying in the dermis. Irradiation inhibits their action and temporarily alters their action. The loss of secretory power is partially due to the direct action of radiation ,partially by cutting off the supply of new cells by interference with cell division and partially to the effect of radiation on the blood supply. For a short period of time there are no cell replacements to compensate for the wear and tear which continually goes on among cells in glandular tissue. With lack of cell replacement the secretion fails.

The action of alpha particles at the level of the epidermal layers represents a complication of action of radiation.[44] It has been shown that the effects of thorium X on skin is due to the alpha particles but that the effects are far beyond the range of these particles in tissue. This action might eventually be explained in terms of formation of new chemicals, by diffusion of the thorium X into the skin through sweat or sebaceous materials, or by summation of radiation action in many adjacent areas including the effects of a marked concentration found both on the surface of and within the epidermis. However, even without an explanation apparent for the action, this example demonstrates a complicating factor that must ultimately be explained in describing the action of radiation on the skin.

When radiation affects the dermal tissue one of the most important phases is the action on the blood vessels. High doses of radiation can produce capillaries that are rigid and fragile[93]

or they may affect the inner lining of cells of the larger vessels as discussed under the section on the circulatory system. Injury to the blood vessels by either process results in loss of blood supply in the region normally supplied by these vessels and this in turn will produce a tissue damage quite apart from the direct action of the irradiation. Lower doses of irradiation may only impair the vessel wall, allowing leakage first of fluid and then of blood cells and finally of whole blood. The extent of this loss is dependent upon the dosage of irradiation suffered.

In general, radiation damage to the skin affects permeability of the capillary blood vessels found in the dermal layers.[93] It is possible to detect radiation damage by the use of this fact. Application of a negative pressure over a defined area of the skin will result in rupture of some of the small vessel walls and small lesions are formed that permit the blood to run into the tissue spaces. These lesions are called petechiae. If a negative pressure is chosen such that 3 or 4 petechiae are formed in one minute, one then has a measurement that permits evaluation of the capillary blood vessel resistance. Over irradiated skin the negative pressure must be increased because the walls of the vessels have become stiffened. By three weeks after irradiation it may be necessary to raise the negative pressure to 50 cm of mercury. If damage has not been too severe to the vessel walls the negative pressure needed to produce the petchiae gradually drops back to normal as the vessel walls are repaired. Permanent fibrosis in the blood vessels can also be detected by this method.

If a blood vessel is blocked as a consequence of radiation, any alternative channels can be used to carry the blood and new vessels may be formed. These new vessels may so increase in number and size as to make a network of fine hollow threads visible to the naked eye.[56]

That the effects of intensive irradiation of the skin are more complex than our discussion would so far indicate is seen if radiation ulcers are produced by x-ray and treated with cortisone. Six thousand "r" applied to the skin of guinea pigs results in deep ulceration. If cortisone is administered 24 hr before irradiation not only is the ulceration eliminated but hair loss is delayed and early erythema is lessened. It is possible that the hormone inhibits the inflammation that occurs and this in turn reduces the secondary effects brought about by the breakdown products in the tissue.[44]

Changes in the dermis, like those in the epidermis, become most conspicuous after long term chronic exposure to irradiation. At first regeneration accompanies the damage, but this balance does not last long. The destructive action dominates and more permanent changes are observed. Blood vessels are altered in form and number and this action is associated with pigmentation or depigmentation. The net result is a contracting scar in which the fibers are more condensed, more abundant and less vascular than the original tissue. The loss of vascularity results in a tissue more susceptible to further injury by such mechanical or physical factors as heat, pressure, or sunburn.[89]

The Reproductive System

The action of radiation on the reproductive system of animals was not only one of the first phenomena investigated using x-ray, but it was also from such studies that the "law of Bergonie and Tribordeau"[12] was first formulated. Since these early observations, work on the effects of radiation on the reproductive system of animals has followed a rather systematic course in numerous laboratories.

Animal experimentation is still the source of most of our information on the effects of radiation on the generative system. Occasionally some information is obtained when the pathologist has the opportunity to examine human tissue removed after previous irradiation. Both types of evidence will be discussed in this section.

The qualitative response is similar for all animals, including man. There may, however, be a marked variation in dose level of radiation required to develop a particular response in different species. This and other biological dif-

ferences make any strict comparison between man and other animals a difficult and sometimes misleading task.

The response of the reproductive system to radiation is only part of the effects seen from irradiation of the genitalia. In 1927 Muller was able to demonstrate that the hereditary material in the chromosomes could be affected by radiation. This effect occurs without producing visible alterations in the organ system. In fact the animal irradiation may have no observable response, but the offspring, many generations removed, will show the radiation effects. Studies of this kind nowadays constitute an entirely new field of research and are generally referred to as radiation genetics.

The human reproductive tract, whether male or female, can be described in the simplest way as simply a series of specialized glands for the production of germ cells and the ancillary tubules to permit fertilization of the germ cells to occur. If fertilization occurs, the complexity of the female reproductive tract increases in that the embryo must develop in the uterus. Maintenance of the embryo depends upon numerous functions within the female that are only indirectly related to the embryo. Such functions include endocrine activity, vascular reactions and nutrition.

The Male System. In the normal male the testes is the organ that produces the germ cells or the sperm. There are in general two types of cells to be considered in the testes. First are the cells of the organ itself. The cells here are fully differentiated and like other muscle, nerve or connective tissue are fairly resistant to radiation. The second type of cell to be considered are the so-called germinal cells, those that give rise to the sperm.

These germinal cells are potentially dividing cells. When division occurs, the daughter cells formed go through a rapid process of differentiation to form the male sperm cell or spermozoa. Very large numbers of sperm cells can be formed by this process.

The fully developed mature sperm cell is almost pure nucleus. The only cytoplasm present is in the organ of motility, the tail. The mature sperm is a completely independent cell, fully differentiated and incapable of further cell division.

The testes is capable of forming very large numbers of sperm. To do this requires a large germinal layer. This large germinal layer is made possible by the presence of hundreds of tubules called seminiferous tubules. Histologically each seminiferous tubule contains three types of cells resting in layers on a basement membrane. Adjacent to the basement membrane are cells called spermatazonia. A second layer of cells is made up of both spermatazonia and spermatids. The third layer of cells contain spermatids and mature spermatozoa or sperm cells. From this description the pattern of the development of the cells appears to be that cells on and in the basement layer divide and these cells then carry out differentiation as they move toward the center of the tubule. This process of differentiation requires two division processes. The first is similar to the type of cell division previously discussed, mitosis. The second type is a special type of division called meiosis by which the chromosomal number is reduced to half the original number (reduction division). The four cells of the second division continue to differentiate into mature sperm cells.

These mature sperm cells are stored in a coiled tubule into which the seminiferous tubules empty. Sperm remain fertile for about seven weeks but are mobile for a much longer period. In man there are about three million sperm available for fertilization of a single ovum for which one sperm is needed. In other animals this number is considerably reduced. For example, the mouse has 17,000 sperm available per ovum while in the fruit fly, Drosophila, the ratio is 16 to 1.[89]

The Female System. The germ cell of the female, the ovum, is formed in the ovary. In a sense the structure of the ovary is the reverse of that of the testes. In the ovary the germinal cells are on the exterior of a nodular shaped structure. Differentiation of the ovum occurs on

the interior of the ovary progressing toward the outside and is ultimately released from the exterior of the gland. Development of the ovum like that of the sperm is a three-step process. For the ovum these steps are oogonia → oocytes → ovum. The differentiation of the ovum follows the same pattern of two different division processes. The principle difference that occurs is that from each daughter cell only one fully developed ovum results. After the chromosomal number has been halved (reduction division) in the ovum, only one cell goes on to develop. The remaining three cells degenerate and are reabsorbed.

Unlike the case of sperm formation, ovum formation is a limited process. In the average human female, one cell develops per month. This cell contains a relatively small amount of nucleus and a large amount of cytoplasm.

The entry of one sperm into one ovum produces a zygote which is a primitive embryonic cell. In this zygote the total number of chromosomes characteristic of the species is regained with half coming from each parent cell. The chromosomes presumably carry the hereditary components of the parental cells and are at least one locus where radiation may have an effect.

Hormonal Influences. In addition to the production of ova or sperm, the ovaries and the testes are organs that release into the blood stream substances which support the secondary structures that serve to identify women from men. In the female these hormone substances are called estrogens; in the male they are called androgens. The exact action of these hormones is not yet understood except that they have some control over growth and development of cells at specific loci in the body. The production and release of these hormone substances in the genital organs is controlled by a feedback mechanism in which the pituitary gland is the second component. This pituitary gland is located approximately in the center of the head directly behind the eyes. The only connection with the gonad tissue is through the blood stream. As in all feedback mechanisms the purpose is to maintain a constant level of input or output. In the case of the ovaries or testes and the pituitary gland the control is maintained in general in the following fashion: release of pituitary hormones stimulates the production of gonadal hormones which in turn suppresses production of pituitary hormones. Women, in keeping with the rest of their nature, complicate this pattern, but do not change it. In women there are two sets of feedback mechanisms which are integrated so as to control not only the production of ova but also control the supporting phenomenon of menstruation.

The importance of this feedback mechanism to the radiobiologist is simply that irradiation of the ovaries or testes may also influence the function of the pituitary and also irradiation of the pituitary may very well cause disturbances in the production of ova or sperm.

Irradiation of the Male and Female Reproductive Systems

The influence of radiation on both the male and female reproductive systems follows much the same pattern. The dividing cells vary in their susceptibility to radiation according to their degree of maturation.[40] Proliferation is highest with the oogonia or spermatagonia. Therefore it is in these cells that the first effects of radiation is seen. This first effect is to simply delay cell division. In the male a dose of radiation of about 300 r or slightly lower will delay sperm production for about three weeks. In the female, the cells are more sensitive and 170 r is sufficient to inhibit the oogonia and cut off the supply of differentiating cells.[89] At these low doses of radiation the cells in both the male and female that have begun differentiation, complete their maturation. However, new daughter cells are blocked and a temporary sterility follows. In the female such an irradiation may be followed by 1 to 3 months of normal menstruation after which menses may be stopped for from 1 to 3 years.[89]

At higher doses of radiation the germinal cells of both the male and the female may be

damaged irreversibly. Hence in females permanent sterilization occurs after about 300 r while castration of the male occurs with about 600 r.

The mature germ cells are the most resistant of the germinal cells. However, even with these cells the resistance to radiation is not constant. Sperm cells show a change in sensitivity depending upon the length of time they have been stored in various parts of the genital tract.[89]

The influence of radiations of various kinds on sterility or fertility has been examined in many species. One generalization that seems to be permitted at this time is that eggs or ova of any one species are more susceptible to radiation than is sperm of the same species. In mice both P^{32} and I^{131} in microcurie amounts reduce fertility in the female before the male is affected.[97] A similar action is seen with whole body x-irradiation administered at very low dose rates (2.5 r per day for 200 days). If a single dose of radiation is given, 170 r will cause sterility and the incidence of estrous[1] is low for 10 months post irradiation. In monkeys the LD 50/30 dose produces changes in the ovaries of the female.[97] In chickens changes in the ovarian follicle start at about 400 r and follicle degeneration at about 800 r. In the roosters, however, injury to the spermatocytes begins at about 1200 r.[96] In fish (Fundulus heteroclitus) eggs exposed to 100,000 r within the body of the female were sometimes fertilizable with normal sperm, while sperm irradiated with 200,000 r and then used to fertilize normal eggs could often produce some normal offspring.[66]

Of course, any action of radiation that might influence the menstrual cycle in humans or the estrous cycle in other animals would also affect fertility since it could influence the course of ovulation. In female rats 400 r of x-ray has such an effect while neutron bombardment at the rate of 3 r per day for 37 days produces definite changes in the estrous cycle.[65]

[1]In many mammals, the period of "heat" or sexual receptivity as well as the process of ovulation is termed "estrous."

If one irradiates the zygote shortly after fertilization, the results obtained are similar to those observed with the ova although irradiation of the zygote is far more damaging than the irradiation of either gamete.[89] This is an observation that is valid not only for radiation but for other agents as well. In the human it is difficult to assess damage to the embryo by radiation since there is no definite way that all abnormalities can be related to radiation damage in a cause and effect way. Doses which cause injury if given in the first month of pregnancy usually lead to death of the embryo and abortion. After the first month the most likely radiation injury is in the central nervous system tissue, in bone growth and in the blood vessels. It is in these structures that the mitosis rate is high at this time. As the embryo grows these systems become more and more radioresistant until in the adult animal the central nervous system represents one system almost inert to action of radiation except at exceptionally high doses of several hundred thousands of r.

Influence of Irradiation on Hormonal Balance

Gonadal effects of radiation can be demonstrated following radiation of the pituitary gland. Here, of course, the feedback system is disturbed by an imbalance imposed at one component of the feedback mechanism, but the net results, namely gonadal changes, are none the less the end result. Low dosage of x-ray to the pituitary in rats has no effect on the sexual development of the immature female. However, if gamma radiation at the level of the LD 50/30 is given, pituitary tumors are formed and this, of course, leads to malfunction of the gland.[97] Neutrons are even more efficient in producing tumors. Only 40–70 rem of neutrons will lead to tumor formation and the maximum incidence of these neoplasms may be from 17 months to two years post irradiation.[97] As the radiation dosage is increased, more severe immediate effects are noted in the pituitary. If high energy deuterons are used, 6300 rep will cause total destruction of the pituitary in nine

months. At 18,900 rep of deuterons, the pituitary is destroyed almost immediately.[96]

More subtle effects of the interaction of radiation and gonadal hormones can be investigated by a process whereby irradiation and administration of the male or female hormones are combined. In such experiments it has been shown that testosterone (the male hormone) inhibits the incidence of tumors formed by irradiation in mice but estradiol (the female hormone) augments the incidence of radiation tumors. If higher doses of irradiation are followed by estrogen treatment, there results a higher mortality than with the irradiation alone.[66] The time of administration of the hormone is important in any such experiment. For example, if estrogens are administered 10 days before mice are irradiated, the hormone improves survival of the animals. This is apparently so because estrogen treatment leads to stimulation of growth of the tissue and by the end of ten days the cells are further along in differentiation and are therefore more resistant to radiation.[66] However, if the estrogen is given only slightly before or at the time of irradiation, the cells are actively dividing and hence more susceptible to radiation. While this answer may be necessary it is certainly not sufficient to explain all the subtle interactions between hormones and radiation. There are still numerous observations to be made and many already made but not understood will require a more complex and detailed analysis for complete understanding.

Radiation Genetics

General Comments. The most reasonable place in which to discuss effects of radiation on chromosomes, genes, and mutation rate is in a discussion of the reproductive system.

To understand the effects of radiation on the genetics of a cell or an organism, a number of concepts about normal cell division should be made clear. In its normal effort to divide, a cell undergoes a great number of very complicated, simultaneous reactions. In a general way this division (mitosis) can be thought of as a very complicated self-replicating servo system. This servo system is made up of an extremely large number of feedback loops. These loops may interact in many ways and still have an end result that appears to represent an equilibrium or near equilibrium condition. However, if one were to look at one single feedback loop as a function of time, it is possible that it might never represent a constant function, but may vary over a wide range of operation. The question then arises as to how far a given feedback loop can vary before the compensatory action of all other associated loops cannot control the system, i.e., before an error in the system can be detected by gross observation. In other words, how far can a system vary and still be considered "normal"?

It is exactly this problem that complicates a study of normal cell division. Sometimes a minor "error" in coordination of two feedback loops leads immediately to the death of the cell. Sometimes what appears to be total disruption of the cell, does not even slow down the normal cell operation. To date it has not been possible to categorize the types of damage that lead to cell death. Therefore, when the effects of a stress such as radiation are studied in cell division, one is restricted to a description of gross changes that occur either in the irradiated system or in the offspring of the irradiated system. Nevertheless one realizes that there may be numerous actions of the radiation that may be disrupted to the cell, but simply cannot be observed or evaluated by our present standards and knowledge.

Numerous excellent reviews are available on the effects of radiation on the genetic composition and behavior of both plant and animal cells[37,49,65,66,83] and if details of the subject are desired these reviews should be consulted. In what follows here an effort will be made to offer only major concepts and observations. It is hoped that the material chosen will at least make the reader aware of the complications of the field, even if it does not answer his questions.

Chromosomal Aberration[37,49,69,84,85]. At low

doses irradiation may do nothing more than simply delay division. This implies that although some injury is inflicted, it is followed by a reparative process during the period between irradiation and mitosis.[86] Once the division begins in a cell, it may take very heavy irradiation to stop the division process. However, even if division is not stopped individual chromosomes may be injured by quite small doses of radiation. Breakage of the chromosome apparently occurs simply because ionizing radiation shakes the chromosomes and by some mechanism transmits enough energy to disrupt the system. Once the breakage has occurred, recovery (restitution) may occur fairly rapidly. Unless the recovery is rapid the damage that is done becomes permanent, either in the form of a permanent break or an abnormal joining.

In the case of the breakage of a single chromosome there are three possible results besides immediate recovery:

(1) Deletion: Part of the chromosome is cut off and becomes a loose part not rejoining the nucleus.

(2) Translocation: The broken part of the chromosome becomes attached to the other end of the same thread.

(3) Inversion: A detached chromosome fragment becomes reattached by its distal end to the thread from which it broke.

When cells are irradiated, the majority probably rejoin and give a restituted chromosome no different than the original. The form of the restituted chromosome obviously depends on the location of the break along the thread and upon the degree of motion of the cell parts. Any circumstance or parameter that favors movement of the chromosome during irradiation, decreases the chance of repair and gives a higher incidence of chromosomal aberration.

The number of simple chromosomal breaks that occur with radiation is dependent upon the dose given. If two breaks occur simultaneously in the same chromosomes, the four broken ends may rejoin in new ways. The portion between the two breaks may be restituted except in reverse order or a ring may be formed by the union of the two ends between the two breakpoints leaving a fragment unattached without a centromere. This fragment will come adrift at division. When the centromeres pull apart at anaphase the chromosome body is incapable of completely dividing and a "bridge" is formed. A similar situation can arise if two different chromosomes are broken and the four ends are in close enough proximity so that one chromosome body has both centromeres and the other fragment has none.

Any of these radiation induced changes in the chromosome may give rise to mechanical difficulties at division that will lead to death of the cell, but this cell can have offspring analogous to gene mutation and these are often a dominant character. The chromosomal aberrations may cause marked damage or infertility in the first generation offspring and in this way are more severe than the radiation induced gene changes that are recessive in nature.[31]

Chromosomal aberrations offer a very convenient and accurate quantitative measure of certain radiation effects. Such experiments are almost ideal for statistical purposes because the chromosomes act as targets where hits can be observed and recorded. From experiments of this kind it appears that gene mutations are no less frequently produced than structural changes, in fact the gene mutations may be more frequent.[89] The type of damage observed in flies or insects is known to exist in many kinds of organisms including man.[31] Exactly how the animal experimentation can be related to man is not yet known; however, it is obvious that when human genetic tissue is exposed to radiation that some changes certainly will occur. The question arises as to what is the permitted maximum dose of radiation for human beings. This question is somewhat complex and will be discussed in some detail in a later section. However, one can say at present that since the radiation effects are cumulative there is no threshold dose and any radiation must be considered as incurring some risk. Accidental exposures of humans to both neutron and gamma irradiation have shown that even after very severe des-

truction of gonadal tissues, by the end of two years there is an incomplete return of sperm formation.[69] How this may effect the offspring of the individual cannot of course be evaluated for several generations.

Gene Mutations. Heritable changes may also be caused by a modification of the gene, *in situ,* that is without changing the location of the gene on the chromosome. In this case there is no visible change in the cell and as a result no way to detect the abnormality except as the effect appears in later generations.[65,66]

Chromosomal aberrations or gene mutations may occur in somatic cells.[77] These changes may lead to local changes but such changes are not completely determinable by present means. However, changes or damage in germ cells (sperm or ovum) lead to consequences that are far more serious than corresponding changes in the somatic cells because the changes may be passed on to the progeny.[63] Only that radiation which affects the germ cells (sperm or ovum) can be considered as influential in production of inheritable mutations.

Gene mutations are known to occur spontaneously. In long-lived organisms such as man there seems to be low probability of the spontaneous change because there is a greater stability of the gene material than that of shorter lived species. If a new mutation arises it will of course suffer genetic death if it is not passed on to a subsequent generation. Some mutations are lethal and may be eliminated from the society by the death of the individual carrying them. (Examples — hemophlilia and muscle dystrophy.)

On the average in a large population the elimination of mutated genes from the society is offset by the spontaneous inception of new mutations. The net result is that the rate of mutation in the entire population is held roughly constant. The majority of spontaneous mutations appear to be minor heritable changes that are not of a serious nature but are nevertheless deleterious in one way or another. A mutation of course can be advantageous to the species.

If damage is done to a gene, the results of this damage may not be apparent for many generations or it may be apparent in only one generation. The uncertainty of when the mutation will become apparent is simply a statistical uncertainty and occurs for the following reasons. When two germ cells are joined to form a zygote, the chromosomes line up in such a way that similar genes are "paired." Since each gene of the pair has come from a different parent, and since each gene carries a factor that will be developed in the growing organism, the genes of a given pair must obviously interact with each other to produce some given end result. If one gene of a pair determines the characteristic in question it is said to be dominant.

If a change or mutation of a dominant nature has affected one of this pair, the influence of the second gene is overshadowed and an alteration appears in the offspring. If the change that occurs by the mutation is a recessive change, that is the change that is not of a dominant nature, the characteristic will not be transmitted to the progeny until the gene is paired with another gene that has undergone a similar alteration. This pairing might happen by some chance quite quickly. It is more likely, however, that many generations may elapse before the conjugation is effected. In this way each individual may carry a far greater number of recessives than he himself acquires in one generation and the majority of recessives probably never come to light at all. The situation might be serious, however, if circumstances such as an elevated irradiated level of the entire population brought about such an addition to the number of recessives that the chance was materially increased for two such genes to combine.

The distinction between dominant and recessive mutations is not always clear and one observes various grades of dominance in actual practice. In some cases the dominance exerted is incomplete and the effect seen in the progeny is intermediate between the typical effect and that observed with the recessive mutation.

Sex Linked Characteristics. Human beings have 48 chromosomes and the number of genes calculated to be 3×10^4 genes per gamete.[89] With such a large number it is virtually impossible to track the course of all mutations. It is possible to simplify the problem, however, by considering only those mutations that are sex linked. About 4 percent of the observable mutations are actually sex linked.[89] The determination of sex is one of the most obvious heritable characteristics associated with the chromosomal action. The method of action of sex determination varies in different species; however, one principle mechanism, which also acts in man, is apparently brought about by dissimilar chomosomes. All ova possess a so-called X chromosome and the male sperm has either an X or a Y chromosome. Fertilization of an ovum by a sperm bearing an X chromosome results in a fertilized egg containing two X chromosomes which will subsequently develop into a female offspring. If the ovum is fertilized by a sperm bearing a Y chromosome, the fertilized egg will have an X and a Y chromosome (XY composition) and will subsequently develop into a male offspring.

The X and Y chromosome, like all other chromosomes, carry genes associated with definite characteristics, some of which are called "conditional dominants." This means that the mutation considered goes to either the male or female offspring only. In this way if one X chromosome carries a lethal mutation and this is mated to a Y chromosome, the resulting male (XY) combination is lethal since the Y chromosome cannot counteract the mutation. If the X (mutated) is mated to an X (normal), the resulting female (XX) combination survives since a normal X chromosome is present to counteract the effects of the mutated X chromosome. By the use of this knowledge a great deal of work in radiation biology has been done by the geneticist in tracing out the effects of radiation on offspring of irradiated animals. It must always be remembered, however, that the picture may not be as simple as we choose to view it. For example, several separate genes may be involved in the transmission of a single characteristic such as is the case for the transmission of eye color.

Mutation Rate. When cells are exposed to radiation a variety of chromosomal aberrations appear and the number of mutations is increased. Radiation induced mutations are exactly the same kind that arise spontaneously. The effect of the radiation is simply to increase the rate at which the mutations occur.

The influence of radiation on mutation rate seems to be remarkably constant over a wide range of species. Experiments have been done on Tradescantia spores,[37] corn, Drosophila (fruit flies)[9] and mice[83] and all show similar results. As a consequence the problem is posed whether man may not also suffer the same effect. A dose of about 50 r doubles the observed mutation rate in an experimental system. This means that the dose or approximately 50 r has produced an induced mutation rate just equal to the spontaneous mutation rate. It makes no difference how the dose is administered, since the effect is dependent only on the total energy over a very wide range.[65] Apparently the effect is also independent of wavelength, dose rate, and of spacing of the dose of radiation.

The Digestive Tract

The Normal Digestive Tract

Both the size and the structure of the alimentary canal are factors that are important to an understanding of the effects of radiation on the digestive tract.

In the human the digestive tract is about 30 ft long while the diameter of the tract varies along the length, with a total surface area about one half of the surface area of the body or about 6 ft^2.

Like the size, the structure of the digestive tract also varies in different parts of the tract. In general, however, the structure of importance to a consideration of radiation effects appears to be simply a basement membrane covered with a single layer of epithelial cells. The basement membrane is pleated in appearance form-

ing a series of crypts and villi. The net effect of this structure is to provide a sheath of epithelial cells whose total surface area amounts to several times the total surface area of the body. The layer of epithelial cells contains cells in all states of cell growth and differentiation; namely, resting cells, mitotic cells, differentiated cells and dying cells. These cells are all mixed together to form the single layer.

Since the epithelial cells are a covering surface along which food stuff move, there is considerable wear and tear on the cells. To maintain the covering in normal form, the rate of cell division (for cell replacement) must be high. These new cells are derived by multiplication of the reserve daughter cells scattered throughout the cell layer.

On the underside and in close proximity to the basement membrane are very fine branches of blood and lymph vessels that connect the digestive system with the other organs of the body. In addition to the blood supply, there are layers of smooth muscle that line the tract. These muscles and the controlling nerve plexuses provide the power to move the food along the digestive tract.

Besides functioning to absorb the food stuffs from the gut, the highly differentiated epithelial cells are capable of secreting juices and fluids into the gut. These juices and fluids are involved in digestion of the food stuffs.

Irradiation of the Alimentary Canal

The epithelial cells of the gut are easily affected by radiation but some regions are more sensitive than others. If one measures sensitivity of gut cells in terms of a threshold injury dose, one finds a different sensitivity distribution than if the sensitivity is gauged by damage done after exposures to above-threshold doses.[89] The difference observed is probably due to varying degrees of success of the different tissues in repair processes that are initiated by the original injury. This point is of some interest because it means that in the gut there is the possibility of producing gross injury in places other than those that receive the highest irradiation dose.

Irradiation of mice or rats with amounts of radiation in the mid-lethal range (approximately 500 r) leads to some interesting results at the level of the intestine.[18] Mitosis is stopped within approxmately one-half hour after irradiation. By 96 hr many cells of the crypts have returned to normal but at this time the epithelium of the villi shows the maximum damage. Apparently the cells of the villi become damaged 48 hr or more after exposure, at a time when the cells of the crypts are being repaired. The animals die when the cells of the villi show their greatest damage. Accompanying the histological changes, there is a decreased absorption of salt from the intestine and indeed the net flow of water in the irradiated animal is from the blood into the intestine while in the control animal the direction is just the reverse. This action results in a dehydration of the animal during about the first three days post irradiation. There is a rehydration following this period with maximum water absorption on about the sixth day post irradiation. During this period of maximum water reabsorption (3rd-6th day) there is a decrease in the rate of uptake of glucose. This appears to mean that the permeability of the intestine is adversely affected even though rate of water passage is increased.

As with other tissues, the first effect of irradiation of the gut is interference with mitotic activity in the epithelial cells. This is followed by cell degeneration which results in a large number of cells being thrown off the basement membrane and the folds or crypts of the gut. The cells of the crypts are extremely sensitive to radiation and the first effects are seen in these cells. The cells of the villi seem to be more resistant.[61] In any case the gut becomes cluttered with these cells and proper function of digestion is stopped.[21,78]

Once radiation damage has occurred, repair proceses are instigated at once. Some areas may well suffer from over-production in the repair process. In this case the replacement cells do not appear, as do the original cells, in a single layer. Rather there are regions where the cells are stacked one on top of another in an untidy

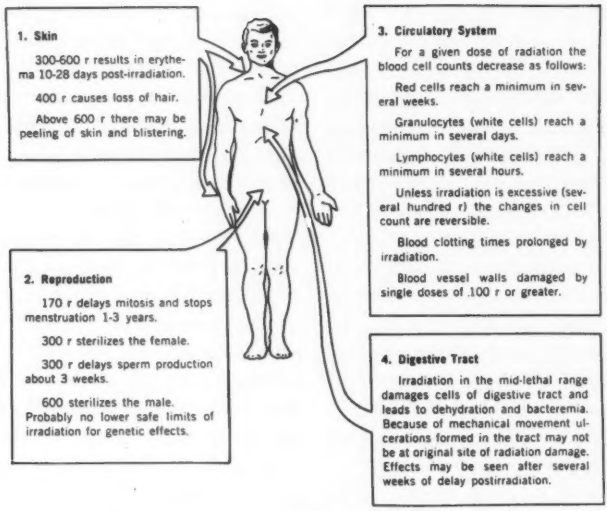

1. Skin
300-600 r results in erythema 10-28 days post-irradiation.
400 r causes loss of hair.
Above 600 r there may be peeling of skin and blistering.
2. Reproduction
170 r delays mitosis and stops menstruation 1-3 years.
300 r sterilizes the female.
300 r delays sperm production about 3 weeks.
600 sterilizes the male. Probably no lower safe limits of irradiation for genetic effects.
3. Circulatory System
For a given dose of radiation the blood cell counts decrease as follows:
Red cells reach a minimum in several weeks.
Granulocytes (white cells) reach a minimum in several days.
Lymphocytes (white cells) reach a minimum in several hours.
Unless irradiation is excessive (several hundred r) the changes in cell count are reversible.
Blood clotting times prolonged by irradiation.
Blood vessel walls damaged by single doses of 100 r or greater.
4. Digestive Tract
Irradiation in the mid-lethal range damages cells of digestive tract and leads to dehydration and bacteremia. Because of mechanical movement ulcerations formed in the tract may not be at original site of radiation damage. Effects may be seen after several weeks of delay postirradiation.

Fig 10. Summary of biological effects of radiation on four organ systems.

mess. These overcrowded areas may alternate with areas where there is a deficiency of cells.[18,21] In this way there are areas of the lining of the gut that are denuded areas and have no power of secretion. In these denuded areas the normally differentiated cells are replaced by connective tissue.

The consequence of even minor damage is an abnormal irritation of cells along a considerable length of gut in the neighborhood of the affected cells. This generally results in an increased movement of the whole intestine causing diarrhea which may or may not be accompanied by the loss of blood into the bowel.

If cell destruction is widespread and affects a large mass of epithelial cells, the tissues beneath the surface layer will be laid bare and an ulcer will be formed. This permits an invasion of bacteria which normally inhibit the gut. The ulceration that is formed is seldom limited to only one area. The irritation that occurs may give rise to such vigorous action of the intestine that further mechanical damage is done elsewhere along the epithelium and this results in a general ulceration all along the intestinal canal.[89]

Bacteremia as a Result of Irradiation. The invasion of bacteria common in the gut but foreign to the blood stream arises many problems in a consideration of the effects of irradiation. In mice and rats the maximum incidence of infection is about 9 days post irradiation. The bacteremia (bacteria in blood stream) parallels the daily death rate of the animals thus indicating that infection is probably a factor in radiation death.[58] Associated with the bacteremia there is, of course, a decrease in the available white blood cells to combat the infection. This makes the bacteria doubly dangerous. The use of antibiotics has been successful in preventing or decreasing radiation deaths attributable to this bacteremia. To date it would appear that streptomyecin is probably the most effective antibiotic for this use.[41,59]

Extra-Intestinal Damage. The action of irradiation is not limited to the intestine. Radiation, whether from radium (x- and γ-rays) strontium (beta particles) or x-ray, lead to a decrease in the gastric emptying time (reduced movement of food into the intestine).[17] This is generally accompanied by vomiting. The time delay before these effects is somewhat depend-

ent on the species, being one day for mice, three days to three weeks for dogs and up to three months post-irradiation in humans.

Summary

The major effects of irradiation on the four organic systems of man discussed in this survey are shown in Figure 10.

For currently *permitted* dosages see Figure 11.

Permitted Tolerance of the Human To Particulate and Electromagnetic Radiations

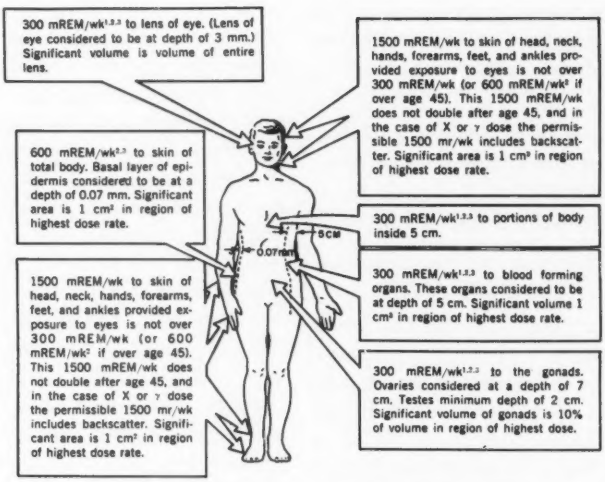
Acompanying an understanding of the effects of ionizing radiations on biological systems, it is convenient to have information on the maximum permissible doses of irradiation for the human. Such a consideration is found in an article entitled "Maximum Permissible Internal Dose of Radionuclides: Recent Changes in Values" by K. Z. Morgan and appearing in *Nucl. Sci. Eng.*, 1, 477-500 (1956). K. Z. Morgan is chairman of the Committee on Internal Dose, of the Committee on Radiation Protection and the Committee on Internal Dose of the International Commission on Radiological Protection. Hence it seemed presumptious to do more than simply abstract his report for the subject matter of this survey.

There are two organizations or committees that concern themselves with tolerance limits of radiation exposure. These committees are the National Committee on Radiation Protection (NCRP) and the International Commission on Radiological Protection (ICRP).

Early recommendations of these committees established two basic standards: ". . . (1) A maximum permissible dose rate of 0.2 r per day (or 1 r/week), and (2) A maximum permissible body burden of radium of 0.1 μg. The 0.1 μg of radium continues to be a maximum permissible body burden (q) of radium and in addition this value is the basic reference for determining the maximum permissible body burden of all alpha emitting, bone seeking isotopes." The rate of 0.2 r day has undergone a number of revisions. In 1936 tolerance dose was lowered to 0.1 r day (or 0.5 r/week) in the USA. Again in 1948 this dose was reduced to 0.3 rem/week. There is no indication that this value establishes a lower limit and it may be changed again in the future.

In Europe the basic dose rate of 0.2 r/day was continued until 1950. However, the actual difference in dose rates between USA and Europe was not really a factor of two as the figures seem to indicate but actually was less than that. The reason for this apparent anomaly was that in Europe the dose rate of 0.2 r day was measured adjacent to the body and included the backscatter, whereas in the United States the dose rate of 0.1 r/day was measured in air. The tendency today in the U.S. is to follow the European practice of dose measurement and make measurements that include backscatter because they relate more directly to the energy delivered to the tissue by ionizing radiation. Even this dosimetry is uncertain at best because the absorbed dose inside the body can be built up through such phenomena as scattering to a maximum that is several times the absorbed dose measured at the surface of the body.

The magnitude of the build-up of dose in the body is dependent upon several factors such as the distance from the source, direction of the incident beam, width of beam, the scattering material present, energy of radiation and finally the units of measurement used. There are a number of units that have been proposed. The r value has, of course, been well defined (r = 1 esu/0.001293 g *air*). The unit rep was introduced in 1944 to measure the absorbed dose in tissue (83-93 ergs/g of soft tissue). This unit was later modified by the International Committee on Radiological units to form the *rad* which is the amount of radiation that produces 100 ergs of energy in one gram of tissue. The need of a unit of absorbed dose is urgent because of the fact that exposure to ionizing radiation other than with x- or gamma rays occurs nowadays. The *rad* unit is very useful in monitoring techniques or in maintaining records, but it should be remembered that it should not be used for reporting experimental data because one must have information on energy delivered per gram (rad) for each type


300 mREM/wk[1,2,3] to lens of eye. (Lens of eye considered to be at depth of 3 mm.) Significant volume is volume of entire lens.
1500 mREM/wk to skin of head, neck, hands, forearms, feet, and ankles provided exposure to eyes is not over 300 mREM/wk (or 600 mREM/wk² if over age 45). This 1500 mREM/wk does not double after age 45, and in the case of X or γ dose the permissible 1500 mr/wk includes backscatter. Significant area is 1 cm² in region of highest dose rate.
600 mREM/wk[2,3] to skin of total body. Basal layer of epidermis considered to be at a depth of 0.07 mm. Significant area is 1 cm² in region of highest dose rate.
300 mREM/wk[1,2,3] to portions of body inside 5 cm.
5CM
0.07mm
1500 mREM/wk to skin of head, neck, hands, forearms, feet, and ankles provided exposure to eyes is not over 300 mREM/wk (or 600 mREM/wk² if over age 45). This 1500 mREM/wk does not double after age 45, and in the case of X or γ dose the permissible 1500 mr/wk includes backscatter. Significant area is 1 cm² in region of highest dose rate.
300 mREM/wk[1,2,3] to blood forming organs. These organs considered to be at depth of 5 cm. Significant volume 1 cm² in region of highest dose rate.
300 mREM/wk[1,2,3] to the gonads. Ovaries considered at a depth of 7 cm. Testes minimum depth of 2 cm. Significant volume of gonads is 10% of volume in region of highest dose.

(1) The 300 mr/wk of X or γ radiation measured in air (when E < 3 Mev) may be increased to 450 mr/wk to the lenses of the eye, and about 400 mr/wk to the bone, and to other tissue more than 5 cm inside the body with exception of the gonads which are limited to 300 mRM/wk until after age 45.

(2) Total body dose rate (including dose rate to the gonads) may be doubled after age 45 provided the lens of the eyes do not receive > 300 mREM/wk from radiation of high specific ionization and > 600 mREM/wk total dose.

(3) An alternate rule Maximum permissible weekly dose of X or γ (E < 3 Mev) radiation may be 300 mr[1,2] measured in occupied area.

Fig 11. Basic permissible exposure rates to external sources of ionizing radiation. Adapted from reference (62).

of radiation in order to define the biological damage.

A unit more applicable to man is the *rem* unit which depends on the relative biological effectiveness of the radiation. The concept of relative biological effectiveness has changed considerably in the last ten years and at present there is consideration of a notion that would set the RBE for alpha and beta radiation equal to a function of the linear energy transfer (LET).

Ionizing radiation, whether from an internal or external source, has damaging characteristics arising from a number of factors. The damage is related to the total absorbed dose, the type of radiations, its LET and also to such factors as the absorbed dose rate, radiosensitivity of the tissue and the importance of the tissue to vital body functions. Because of such factors, no simple single dose statement may be made, but rather the permitted dose will differ with different organs and different parts of the body. These relations are best shown in the form of a figure. See Figure 11.

It can be seen that the principle organs of the body which limit the radiation exposure of the body are (1) blood-forming organs, (2) eyes, (3) gonads and (4) skin. It must be remembered that any one of these organs may

[1]As an illustration of the fluidity of the problem of defining maximum permissible dose limits of radiation, it is of interest to note that during the period in which this survey was in the process of publication, a notice of a proposed change in dosage limits was issued by the AEC. The "Notice of proposed rule making, Statement of Consideration" dated April 24, 1959 ". . . would permit occupational exposure to the whole body, gonads and blood forming organs over a period of a year not exceding one-third the annual exposure to radiation permitted under the existing requirements". The complete proposed rule changes are rather complex and for detailed information one should consult a new NBS Handbook 69 now being published on "Maximum Permissible Amounts of Radioisotopes in the Human Body and Maximum Permissible Concentrations in Air and Water."

limit the external exposure depending upon the type of radiation, its anglar distribution, its energy, the distance from the source, and the local shielding that can be provided.

With the extended use of radioisotopes the question of maximum permitted concentration of an internally absorbed dose becomes of importance. The only official source providing information on the maximum permissible body burden (q) and the maximum permitted concentrations (MPC) of isotopes are the Handbook 52 and the ICRP handbook. All values of MPC now published refer to continuous exposure. The critical body organ is that organ of the body that results in the greatest damage to the body. The critical organ may not receive the greatest concentration of isotope nor need it necessarily be the organ showing the greatest damage. However, the greatest concentration or the greatest damage are generally reliable indicators of the critical organ.

It is generally assumed in biology that any isotope taken internally is eliminated exponentially with a biological half life T_b. Since the radioactive half life is T_r, the effective half life in the body is $T = T_b T_r/(T_b + T_r)$. Because of this the MPC is chosen such that the isotope equilibrium is reached in a few weeks or months after which the absorbed dose rate in the critical body organ remains constant at the permissible dose level of 0.3 rem/week. In the case of a few isotopes such as Ra^{226}, Pu^{239} and Sm^{151} it would require more than a normal life span to reach equilibrium. In these cases the MPC is chosen so that the dose rate becomes 0.3 rem/week after 70 years of exposure.

If one considers alpha emitting isotopes or bone seeking isotopes some special problems are encountered. Rather than specify the permitted dose in terms of the concentrations in air and water that will give rise to an absorbed dose rate to the bone of 0.3 rem/week, the maximum permitted dose is based on the amount of isotope that will give the same radiation to the bone as 0.1 μg of $Ra.^{226}$ Actually, 0.1 μg of Ra^{226} absorbed in the bone gives a radiation dose of about 0.8 rem/week which is about three times higher than is desirable. This quantity may well be changed in the future. When one is concerned with bone seeking isotopes other than the radium series, additional corrections must be made for the maximum permissible dose. One such correction is to use a weighted energy value. This value is $\Sigma E(\mathrm{RBE})N$ where N is a nonuniform distribution factor or better still a "relative hazard" factor that one determines experimentally. The value of N is set equal to 5 for the particulate component (d, β^+, β^-, e^- and heavy recoils) for all bone seeking isotopes with the expection of Ra^{226} and P^{32}. This value of 5 was arrived at from experiments that seemed to show that such isotopes as Sr^{89}, Sr^{90} and Pu^{239} produced about 5 times the damage per rad as Ra^{226}. The value of the factor N is rather arbitrarily chosen. It is a complex correction that contains "... (1) nonuniform distribution, (2) radiosensitivity, and (3) essentialness of the body organ." These factors were recognized from experiments that showed that the total energy or gram-rad absorbed dose delivered to the organ may be responsible for most of the biological damage rather than the rad absorbed dose to small portions of the organ receiving the highest absorbed dose. In other words if the isotope is uniformly distributed in an organ it may be more damaging than if "hot spots" occur.

There is contrasting evidence to this that must also be considered. Apparently if 1 μg amounts of Pu^{239} are implanted into the muscles of animals there is a much higher incidence of tumors at the site of implant than if 1 μg of Pu^{239} were deposited throughout the bone. Thus one sees that the problem is somewhat complex.

Accurate determination of the maximum permitted dose for isotopes can be seen to depend upon two factors, the RBE and the value of N. Both of these factors are determined experimentally and hence as better values are obtained, more accurate dosages can be specified. To demonstrate this effect an example might be useful. If the estimate for $(\mathrm{RBE})N$ for

alpha radiation in the bone should turn out to be 4 instead of 50, then the presently accepted permissible dose for Pu^{239} would be reduced from 0.8 to 0.06 rem/week. There seems to be little conclusive evidence that the value of *N* should be changed. Likewise, there is little or no evidence that the RBE of alpha radiation for chronic exposure should be reduced. On the contrary, from a number of animal experiments that used shortening of the life span as a measure, it would appear that the RBE for alpha radiation should be about 60, and 6 for fast neutrons. This is contrasted with 20 and 2 respectively that have been suggested. (If the functional relationship between RBE and LET is used the RBE for 5 Mev alpha particles is 15.) Obviously one must await more data, particularly those from chronic animal studies, to make an accurate evaluation of the maximum permitted dose.

One should understand that with the increased use of isotopes, the presence of nuclear reactors in both universities and industry, and with fall-out from the test of nuclear weapons, there are many problems that must be faced, and many rules that must be laid down even though it is recognized that there is insufficient information to do a complete and accurate job. Toward this end the ICRP in April of 1956 set forth a series of general recommendations. These can be summarized as follows

"... (1) The basic permissible absorbed dose rate will continue to be 0.3 rem in a week for occupational exposure. In exceptional cases, this weekly absorbed dose may be increased by a factor that might be as large as 10 provided the integrated absorbed dose during the 13-week period following the beginning of the higher rate is not greater than 3.0 rem.

"(2) The absorbed dose to each occupationally exposed individual is not to exceed 5 rem/year averaged over a 10 year period. This is intended to limit the absorbed dose to 50 rem by the age of 30 and to 200 rem by the age of 60.

"(3) The permissible exposure rates for prolonged exposure in areas in the neighborhood of controlled areas are to be 1/10 of those permitted within the controlled areas.

"(4) Until more data are available and general agreement is reached, it is considered prudent to limit the permissible genetic absorbed dose to large populations to be of the order of natural background in presently inhabited regions of the earth."

TABLE III

Background Data on Absorbed Dose to Man to Age 30

(Adapted from reference 62)

	Estimates (rads)	
Source of Radiation	*Ovary*	*Testes*
K^{40}	0.39	0.60
Cosmic ray at 0° G lat and sea level	0.72	0.72
Cosmic ray at 50° G lat and sea level	0.82	0.82
Cosmic ray at 0° G lat and 2000 m	1.2	1.2
Cosmic ray at 50° G lat and 2000 m	1.4	1.4
From ground air and buildings	1.2-1.6	1.4-2.0
C^{14}	(0.11 rem)	(0.11 rem)
Totals	2.37-3.45	2.78-4.0

This natural background at present (1955-56) is interpreted as a dose to the gonads of 2-4 rem at the age of 30. This means the ICRP recommendation would permit exposure of large populations to 2 to 4 rem above background to the age of 30. Since in mice at least 50 rem somewhat more than doubles the mutation rate, the permitted dosage rate would not significantly affect the normalcy of the population.

It might be interesting to consider the sources of the natural background and the relative contribution of each component. This is best seen in Table III.

In addition to the general recommendations concerning radiation dosage rate, changes in the maximum permitted concentrations were made by the ICRP. These changes apply specifically to the internal dose and may be summarized as follows:

". . . (1) MPC values for some 70 additional radionuclides will be added to those already in the ICRP Handbook.

"(2) The MPC values for Rn^{220} and Rn^{222} will be reduced by a multiplication factor of 1/3 to make them equal to the old European values.

"(3) The MPC values for all radionuclides that are rather uniformly distributed in the body, i.e., where total body or body water is the critical organ, will be reduced by a multiplication factor of 1/3.

"(4) All the terms used in the calculation of MPC values will be checked and revised if need be.

"(5) A special committee will study and make final recommendations relative to the application of a power function representation of q (body burden) rather than the exponential function that is now used. ($q = AT^{-B}$ rather than $q = q_0\, e^{-0.693}$.)

While the present recommendations set many patterns that will be followed, there are still many problems to be faced. It might be well simply to list some of the current problems.

". . . (1) The selection of maximum permissible intake (MPI) values for a single exposure.

"(2) The selection of MPI values that are safe for human tracer studies.

"(3) The selection of MPC values based on exposure to the gonads.

"(4) The consideration of the influence of secondary factors in the establishment of MPC values for waste disposal.

"(5) The beginning of a number of chronic biological studies with radionuclides."

It appears at present that the MPC values will probably be based on the number of microcuries that can be taken into the body in a single event that will deliver to the critical body organ 0.3 rem/week or 5 rem/year whichever gives the smaller MPC values.

Because of the previous recommendation that the MPC value to large population must deliver an absorbed dose to the gonads of the order of natural background, it should be apparent why MPC values based on gonad exposure must be investigated. While one can use some arbitrary value such as 1/1000 of the MPC values for occupational exposure, the problem is actually somewhat more complex than this. The absorbed dose to the gonads consists of two types of exposure: (1) direct exposure from the isotopes deposited in the gonadal tissue and (2) indirect to gonads from the isotopes in other parts of the body, particularly from the lower end of the large intestine.

Secondary radiation factors may well become the limiting problem in determining MPC. How these secondary factors may operate can be seen from some examples. Certain isotopes are concentrated in fish. If fish living in contaminated water were the principle source of food for a given population, it would be neccesary to reduce the MPC values by 100 times over the value that would be acceptable if the population were only consuming the contaminated water itself.

In England it has been observed that certain isotopes (radionuclides) from disposal operations are concentrated in seaweed. This sea-

weed in turn is gathered and eaten by a number of people living in Wales. Obviously, if one is concerned with the importance of low level radioactive waste deposit or contamination of the environment as a result of weapon testing, there is a great deal of ecological work that must be done before rigorous conclusions may be drawn. Examples of this problem are numerous. It is known that some radioisotopes are concentrated in some organisms to the extent of about 10^5. This means that rather low level waste may be concentrated to a point where one or more steps in the food chain are damaged so that there is no longer a balance between the various animal forms. As a result of this imbalance the forests, grazing lands and even wheat crops may suffer damage. This, of course, directly affects man. Such damage may take many years to rectify. While the probability of such action occurring in our present society is perhaps remote, it nonetheless is a factor that must constantly be considered.

REFERENCES

1. ALLEN, A. O., Radiation chemistry of aqueous solution. *J. Phys. Colloid Chem.*, 52, 479 (1948).
2. ALLEN, A. O., Chemical effects of radiation in aqueous solutions. Conference on Biological Applications of Nuclear Physics. Brookhaven National Laboratories, Associated Univ. Inc., Upton, New York (July 1948).
3. ALLEN, J. G., SANDERSON, M., MILHAM, M., KIRSCHAN, A., and JACOBSON, L. D., Heparinemia: An anticoagulent in the blood of dogs with hemorrhagic tendency after total body exposure to roentgen rays. *J. Expl. Med.*, 87, 71 (1948).
4. ALPEN, E. L. and SHELINE, G. E., The combined effects of thermal burns and whole body x-irradiation on survival time and mortality. *Ann. Surg.*, 140, 113 (1954).
5. ALPEN, E. L., ALEXANDER, J. A., and DAVIS, A. K., Combined effects of total body x-irradiation and radiant energy thermal burns on the osmotic and mechanical fragility of the erythrocyte. *Am. J. Physiol.* 179, 541 (1954).
6. BACHEM, A., Physical and biological observations on skin reaction. *Radiology*, 9, 241 (1927).
7. BACQ, Z. M. and ALEXANDER, P., *Fundamentals of Radiobiology*. Butterworth Scientific Publications, London (1955).
8. BAGG, H. J. and HALTER, C. R., Experimental studies on tisue reaction to radiation. *Am. J. Roentgenol. Rad. Ther.*, 24, 640 (1930).
9. BAGG, H. J. and HALTER, C. R., Experimental studies on tissue reaction to radiation. *Am. J. Roentgenol. Rad. Ther.*, 27, 1 (1932).
10. BARRON, *E. S. G.* and DICKMAN, S. R., Studies on the mechanism of ionizing radiations—II. Inhibition of sulfhydrol enzymes by alpha, beta and gamma rays. *J. Gen. Physiol.*, 32, 595 (1949).
11. BARRON, E. S. G., The effect of x-ray on systems of biological importance. *In* A. HOLLAENDER (Ed.), *Radiation Biology*, Vol. I, Chap. 5, McGraw-Hill, New York (1954).
12. BERGONIA, J. and TRIBONDEAU, L., Interpretation de quelques resultats de la radiotherapie et essai de fixation d'une technique rationnelle. *Comp. Rend. Acad. Sci.* (Paris), 143, 983 (1906).
13. BLOOM, W. and BLOOM, M. A., Histological changes after irradiation. *In* A. HOLLAENDER (Ed.), *Radiation Biology*, Vol. I, Chap. 17, McGraw-Hill, New York (1954).
14. BLOUNT, H. C. and SMITH, W. W., The influence of thyroid and thiouracil on mice exposed to roentgen radiation. *Science*, 109, 83 (1949).
15. BUTLER, E. G., The effects of radium and x-ray on embryonic development. *In* B. M. DUGGAR (Ed.), *Biological Effects of Radiation*, Chap. 11, McGraw-Hill, New York (1936).
16. CHASE, H. B. and POST, J. S., Damage and repair in mammalian tissues exposed to cosmic ray heavy nuclei. *J. Av. Med.*, 27, 533 (1956).
17. CONRAD, R. A., Effects of gamma radiation on gastric emptying time in the dog. *J. Appl. Physiol.*, 9, 234 (1956).
18. CONRAD, R. A., Some effects of ionizing radiation on the physiology of the gastrointestinal tract: A review. *Radiation Research*, 5, 167 (1956).
19. CORK, J. M., *Radioactivity and Nuclear Physics*, 2nd edn. Chaps. 4, 5, 6, and 7, D. Van Nostrand, New York (1950).
20. COURT BROWN, W. M. and ABBOTT, J. D., The incidence of leukemia in ankylosing spondylitis treated with x-rays: A preliminary report. *Lancet*, 1, 1283 (1955).
21. CRONKITE, E. P., JACOBS, G. L., BRECKER, G., and DILLIARD, G., The hemorrhagic phase of the acute radiation syndrome due to exposure of the whole body to penetrating ionizing radiation. *Am. J. Roentgenol. Rad. Ther.*, 67, 796 (1952).
22. CRONKITE, E. P., Some effects of ionizing radiations on human beings Report TID 5358, GPO Washington (1956).
23. DALE, W. M., The effect of x-rays on the conjugated protein d-amino acid oxidase. *Biochem. J.*, 36, 80 (1942).
24. DALE, W. M., DAVIES, J. V., and MEREDITH, W. J., Further observations on the protection effect in radiation chemistry. *Brit. J. Cancer*, 3, 31 (1949).
25. DALE, W. M. and DAVIES, J. V., The deamination of aqueous solutions of L-serine by x-radiation. *Nature*, 166, 1121 (1950).
26. DALE, W. M., Basic radiation biochemistry. *In* A. HOLLAENDER (Ed.), *Radiation Biology*, Chap. 4, McGraw-Hill, New York (1954).
27. DAVIDSON, H. O., JR., Biological effects of whole body gamma radiation on human beings (U). Operations Research Office, Johns Hopkins Univ., Technical Memorandum ORO-T-357 (December 1956).
28. DAVIS, A. K., ALPEN, E. L., and SHELINE, G. E., The combined effects of thermal burns and whole body irradiation—II. Anemia. *Ann. Surg.*, 140, 726 (1954).
29. DUSHMAN, S., *Fundamentals of Atomic Physics*. McGraw-Hill, New York (1951).
30. ELLINGER, F. P., Radiation sickness. *In* Conference on Biological Applications of Nuclear Physics,

31. EVANS, R. D., Quantitative inferences concerning the genetic effects of radiation on human beings. *Science*, 109, 299 (1949).

32. FAILLA, G., Ionization and its bearing on the biological effects of radiation. *In* B. M. DUGGAR (Ed.), *Biological Effects of Radiation*, Chap. 3, McGraw-Hill, New York (1936).

33. FANO, U., Principles of radiological physics. *In* A. HOLLAENDER (Ed.), *Radiation Biology*, Chap. 1, McGraw-Hill, New York (1954).

34. FRANK, J. and PLATZMAN, R., Physical principles underlying photochemical radiation—chemical and radiobiological reactions. *In* A. HOLLAENDER (Ed.), *Radiation Biology*, Vol. I, Chap. 3, McGraw-Hill, New York (1954).

35. FRIEDENWALD, J. S. and SIGELMAN, S., The influence of ionizing radiation on mitotic activity in the rat's corneal epithelium. *Expl. Cell. Res.* 4, 1 (1953).

36. FRIEDLANDER, G. and KENNEDY, J. W., *Nuclear and Radiochemistry*, Chaps 3-7. John Wiley, New York (1955).

37. GILES, N. H., JR., Radiation-induced chromosome aberrations in *Tradescantia*. *In* A. HOLLAENDER (Ed.), *Radiation Biology*, Chap. 10, McGraw-Hill, New York (1954).

38. GLASSER, O., QUIMBY, E. H., TAYLOR, L. S., and WEATHERWAX, J. L., *Physical Foundations of Radiology*. Paul B. Hoeber, Inc., Medical Book Dept. of Harper, New York (1947).

39. GLASSTONE, S., *Sourcebook on Atomic Energy*. Chap. 7, Van Nostrand Co., Inc., Princeton, New Jersey (1958).

40. HALBERSTAEDTER, L. and ICKOWICZ, N., The early effects of x-ray on ovaries of the rat. *Radiology*, 48, 369 (1947).

41. HAMMOND, C. W., The treatment of post-irradiation infection. *Radiation Research*, 1, 448 (1954).

42. HANDBOOK 62. Report of the International Commission on Radiological Units and Measurements. (ICRU). U.S. Dept. of Commerce, National Bureau of Standards (1956).

43. HICKS, S. P., Effects of radiation on the embryo and fetus. In Report of the Committee on Pathological Effects of Atomic Radiation, Publication 452, National Acad. of Sci., Nat. Res. Council, Washington (1956).

44. HOUGHTON, L. E., WALTER, J. B., and JONES, D. E. A., The inhibition of acute x-ray damage with cortisone. *Brit. Med. J.*, 2, 1313 (1954).

45. HUMBLE, J. G., JAYNE, J. H. W., PULVERTAFT, R. S. V., and WILSON, C. W., The effects of irradiation on human lymphocytes. *J. Fac. Radiologists*, 5, 227 (1954).

46. JACOBSON, L. O., SIMMONS, E. L., MARKS, E. K., GASTON, E. O., ROBSON, M. J. and ELDREDGE, J. H., Further studies on recovery from radiation injury. *J. Lab. Clin. Med.*, 37, 683 (1951).

47. JACOBSON, L. O., The hematological effects of ionizing radiation. *In* A. HOLLAENDER (Ed.), *Radiation Biology*, Chap. 16, McGraw-Hill, New York (1954).

48. KAMEN, M. D., *Isotopic Tracers in Biology*, 3rd ed. Academic Press, New York (1957).

49. KAUFMAN, B. P., Chromosome aberrations induced in animal cells by ionizing radiation. *In* A. HOLLAENDER (Ed.), *Radiation Biology*, Chap. 9, McGraw-Hill, New York (1954).

50. KNOWLAND, N. P., JR., LEIFER, E., HOGNESS, J. R., HEMPELMANN, L. H., BLANEY, L. F., GILL, D. C., OAKS, W. R., and SHAFER, C. L., Beta ray burns of human skin. *J. Am. Med. Assoc.*, 141, 239 (1949).

51. LANGE, R. D., MALONEY, W. C., and YANIAWAKI, T., Leukemia in atomic bomb survivors—I. General observations. *Blood*, 9, 574 (1954).

52. LANGE, R. D., WRIGHT, S. W., MATSUOKA, S., and MATSUNAGA, H., Refractory anemia occurring in survivors of the atomic bombing in Nagasaki, Japan. *Blood*, 10, 312 (1955).

53. LEA, D. E., *Action of Radiation on Living Cells*. Cambridge University Press, London. (The Macmillan Co., New York), (1947).

54. LEDDY, E. T. and WEATHERWAX, J. L., Erythema dose as the limit in deep roentgen therapy dosimetry. *Am. J. Roentgenol. Rad. Ther.*, 12, 514 (1924).

55. LIEBOW, A. A., WARREN, S., and DE COURSEY, E., Pathology of atomic bomb casualties. *Am. J. Pathol.*, 25, 853 (1949).

56. MERWIN, R. M. and HILL, E. L., Effect of local roentgen irradiation on the formation of new capillaries after injury. *J. Natl. Cancer Inst.*, 15, 103 (1955).

57. MILLER, N., Oxidation of ferrous ions in aqueous solution by x- and γ-radiation. *Nature*, 162, 448 (1948).

58. MILLER, C. P., HAMMOND, C. W., and TOMPKINS, M., The incidence of bacteremia in mice subjected to total body x-radiation. *Science*, 111, 540 (1950).

59. MILLER, C. P., HAMMOND, C. W., and TOMPKINS, M., Reduction of mortality from x-radiation by treatment with antibiotics. *Science*, 111, 719 (1950).

60. MOLONEY, W. C. and LANGE, R. D., Leukemia in atomic bomb survivors—II. Observations on early phases of leukemia. *Blood*, 9, 663 (1954).

61. MONTAGNA, W. and WILSON, J. W., A cytological study of the intestinal epithelium of the mouse after total body x-irradiation. *J. Nat. Cancer Inst.*, 15, 1708 (1955).

62. MORGAN, K. Z., Maximum permissable internal dose of radionuclides. Recent changes in values. *Nucl. Sci. Eng.*, 1, 477 (1956).

63. MULLER, H. J., The production of mutations by x-rays. *Proc. Natl. Acad. Sci., U.S.*, 14, 714 (1928).

64. MULLER, H. J., An analysis of the process of structural changes in chromosomes of Drosophila. *J. Genetics*, 40, 1 (1940).

65. MULLER, H. J., The manner of production of mutations by radiation. *In* A. HOLLAENDER (Ed.), *Radiation Biology*, Chap. 8, McGraw-Hill, New York (1954).

66. MULLER, H. J., The nature of the genetic effects produced by radiation. *In* A. HOLLAENDER (Ed.), *Radiation Biology*, Chap. 7, McGraw-Hill, New York (1954).

67. MURPHY, J. B., Experimental studies in roentgen ray effects. *Am. J. Roentgenol. Rad. Ther.*, 11, 544 (1924).

68. NORDSEN, N. G., Blood changes in radiologic work. *Acta Radiologica*, 27, 416 (1946).

69. OAKES, W. R. and LUSHBAUGH, C. C., Course of testicular injury following accidental

exposure to nuclear radiations: Report of a case. *Radiology,* 59, 737 (1952).

70. PACKARD, C., The biological effectiveness of x-ray wave lengths. *In* B. M. DUGGAR (Ed.), *Biological Effects of Radiation,* Vol. I, Chap. 13, McGraw-Hill, New York (1936).

71. PAINTER, E. E. and BRUES, A. M., The radiation syndrome. *New England J. Med.,* 240, 871 (1949).

72. PARKER, H. M., The dependence of the backscattering of roentgen rays in a phantom on focal distance, quality of radiation and field size. *Acta Radiol.,* 16, 705 (1935).

73. PATT, H. M. and BRUES, A. M., The pathological physiology of radiation injury in the mammal—I. Physical and biological factors in radiation action. *In* A. HOLLAENDER (Ed.), *Radiation Biology,* Vol. I, Chap. 14, McGraw-Hill, New York (1954).

74. PATT, H. M., Protective mechanisms in ionizing radiation injury. *Physiol. Reviews,* 33, 35 (1953).

75. PATT, H. M., STRAUBE, R. L., TYREE, E. B., SWIFT, M. N., and SMITH, D. E., Influence of estrogens on the acute x-irradiation syndrome. *Am. J. Physiol.,* 159, 269 (1949).

76. POHLE, E. A., and BUNTING, C. H., Skin reactions following exposure to roentgen rays. *Radiology,* 13, 497 (1929).

77. PUCK, T. T., MORKOVIN, D., MARCUS, P. I., and CIECIURA, S. J., Action of x-rays on mammalian cells—II. Survival curves of cells from normal human tissue. *J. Expl. Med.,* 106, 485 (1957).

78. QUASTLER, H., The nature of intestinal radiation death. *Radiation Res.* 4, 303 (1956).

79. QUIMBY, E. H. and ARNESON, A. N., A comparison of paraffin and water phantoms for roentgen-ray depth dose measurements. *Am. J. Roentgenology,* 37, 93 (1937).

80. QUIMBY, E. H. and PACK, G. T., Skin erythema for combinations of gamma and roentgen rays. *Radiology,* 13, 306 (1929).

81. RICHARDS, A. G., The production of erythema of the skin by exposure to x-ray radiation. *J. Dental Res.,* 34, 100 (1955).

82. ROBINSON, J. N. and ENGLE, E. T., Effect of neutron radiation on the human testes: A case report. *J. Urol.,* 61, 781 (1949).

83. RUSSELL, W. L., Genetic effects of radiation in mammals. *In* A. HOLLAENDER (Ed.), *Radiation Biology,* Vol. I, Chap. 2, McGraw-Hill, New York (1954).

84. SAX, K., An analysis of x-ray induced chromosomal aberrations in Tradescantia. *Genetics,* 25, 41 (1940).

85. SAX, K., Types and frequencies of chromosomal aberrations induced by x-ray. Cold Springs Harbor Symposium on Quantitative Biology, 9, 93 (1941).

86. SCHJEIDE, O. A., MEAD, J. E. and MYERS, L. S., JR., Notions on Sensitivity of Cells to Radiation. UCLA School of Medicine, A. E. P., UCLA 348, Contract No. AT-041-Gen 12 (October 1955).

87. SIRI, W. E., *Isotopic Tracers and Nuclear Radiations.* Part I. McGraw-Hill, New York (1949).

88. SOMMERS, S. C., Endocrine changes after hemeadrenalectomy and total body irradiation in parabiotic rats. *J. Lab. and Clin. Med.,* 42, 396 (1953).

89. SPEAR, F. G., *Radiation and Living Cells.* John Wiley, New York (1953).

90. SPENCER, W. P. and STERN, C., Experiments on the validity of the linear relation of mutation frequency to x-ray dose in Drosophila melanogoster. *In* H. A. BLAIR (Ed.), *Biological Effects of External Radiation,* Chap. 7, McGraw-Hill, New York (1954).

91. ST. STENDER, H. and ELBERT, O., Experimental investigations in animals on the behavior of some blood coagulation factors after total irradiation with massive doses. *Strahentherapie* 90, 625 (1953).

92. STENSTROM, W. and MATTICK, W. L., Study of skin reactions after divided roentgen ray doses. *Amer. J. Roentgenol. Rad. Ther.,* 15, 176 (1928).

93. SZENES, T., The evaluation of radiation damage to the skin as determined by measuring the capillary resistance. *Forschi a.d. Geb. d. Roentgenstrahlen,* 82, 614 (1955).

94. THOMAS, M., TAYLOR, H. D. and WETHERBY, W. D., Studies on x-ray effects—II. Stimulative action on lymphocytes. *J. Expl. Med.* 29, 75 (1919).

95. TIMOFEEFF-RESSOVSKY, N. W., ZIMMER, K. G., and DELBRUCK, M., Uber die Natur red Genmutationen und der Genstruktur. *Nachr. Ges Wiss. Gottingen,* 1, 189 (1935).

96. TOBIAS, C. A., VAN DYKE, D. C., SIMPSON, M. E., ANGER, H. O., HUFF, R. L. and KONEFF, A. A., Irradiation of the pituitary of rats with high energy deuterons. *Am. J. Roentgenol.,* 72, 1 (1954).

97. UPTON, A. C. and FURTH, J., Induction of pituitary tumors by means of ionizing radiation. *Proc. Soc. Expl. Biol. Med.,* 84, 255 (1953).

98. WEISS, J., Radiochemistry of aqueous solutions. *Nature,* 153, 748 (1944).

99. WIRTH, J. E. and RAPER, J. R., Reactions of human skin to single doses of beta rays. *In* R. E. ZIRKLE (Ed.), *Biological Effects of External Beta Radiation,* Chap. 12, McGraw-Hill, New York (1951).

100. WITTEN, V. H. and SULZBERGER, M. B., The mode of action of thorium X on human skin. *Am. J. Roentgenol.,* 74, 90 (1955).

101. YOUNG, M. E. J., *Radiological Physics.* Academic Press, New York (1957).

102. ZIRKLE, R. E., The radiobiology and importance of linear energy transfer. *In* A. HOLLAENDER (Ed.), *Radiation Biology,* Chap. 6, McGraw-Hill, New York (1954).

The Influence of Control Gain in a First-Order Man-Machine Control System

CLARENCE L. TIPTON and **HENRY P. BIRMINGHAM,** U.S. Naval Research. Laboratory

An experiment was conducted to observe the effect of varying control sensitivity in a velocity control system. A single sine wave of 0.05 cps was used as the course input, and the subjects tracked in the compensatory mode using a pressure control. The operator was required to apply a maximum force of one ounce to stay on target when tracking with a maximum control gain, whereas eight pounds of force were required with a minimum control gain. Eight naval enlisted men received eight test runs on eight control sensitivities covering a range of 128 to 1. Test runs were one minute in length. A region of minimum error occurred at the lower control sensitivities. The overall error variation was 2.5 times for the entire 128 to 1 range of control sensitivities. The maximum average tracking error did not exceed one percent of the input amplitude.

In the design of man-machine control systems, the question of what is the "optimum" amount of control sensitivity frequently arises. Where the general nature of the course or system forcing function and the dynamics of the system are known, the maximum control force or displacement required of the human can be determined and will be a function of stick sensitivity. Helson[5] and others (Hartman[3], Hartman & Fitts[4], Helson & Howe[6], Jenkins & Connor[7], Searle & Taylor[8]) have studied the influence of control sensitivity in a zero-order or positional type system. This type of control, with no course input, provides a direct relationship between the position of the control stick and the position of the displayed tracking cursor. In general, it is found that performance is optimum over some portion of the lower ranges of control sensitivity, i.e. where the operator is required to supply greater amounts of force and/or displacement as opposed to lesser amounts.

The purpose of the present study is to investigate the effect of changes in control stick sensitivity upon tracking performance when using an isometric or "pressure" stick and a pure first-order (velocity) control system. In this type of control system the relationship between the control stick and the display is such that the rate of cursor movement is directly proportional to stick position. Relative to the differences in system order, Chernikoff and Taylor[2] have demonstrated that velocity control is superior to position control at the lower course frequencies in both the pursuit and compensatory modes of tracking. It remains to be seen, however, whether a distinct optimum value of control sensitivity occurs in a velocity control system or whether some range of optimum values of control gains occur as in the case of Helson's study with a positional system.

METHOD

Apparatus

A block diagram of the velocity control system is presented in Figure 1. A single sine wave of 0.05 cps was the course input and the subject tracked in the compensatory mode using a pressure type control. Finger pressure caused a slight bending of the control lever, which was transduced into an electrical signal by a strain gauge attached to the base of the lever. The sensitivity of this control was variable over a range of 1:128. With a maximum control sensitivity the operator was required to apply a force of 1 oz to cancel the maximum course displacement, whereas, a force of 8 lb was required when operating with a minimum control sensitivity. The movement of the control lever varied from an imperceptable amount at the maximum control sensitivity to approximately $\pm\frac{1}{8}$ in. at the minimum control sensitivity. A ten-channel analog computer provided the necessary electronic transformations for instrumenting the experimental system as well as cumulating error scores.

Error was integrated without regard to sign for each run and the integrated error score was displayed to the experimenter as a reading on a voltmeter.

Procedure

Eight naval enlisted men served as subjects in tracking 8 conditions of control sensitivity. Sensitivities of 1, 2, 4, 8, 16, 32, 64, and 128 were used. Test runs were 1 minute in length with the last 55 seconds being scored. Subsequent to 8 training trials on each condition, the subjects received 8 test runs on each of the above control gains for a total of 64 test runs. A given subject received one test trial on each condition at each test session with the order varied according to a permuted latin square design.

RESULTS AND DISCUSSIONS

A plot of the averages of the integrated error scores for each test condition is presented in Figure 2. Each plotted point represents the average of 64 integrated error scores. The statistical significance of the differences for the various conditions as measured by the sign test (Wilcoxin[9]) are presented in Table I.

Corroborating Helson[5], the performance curve is slightly J-shaped with a broad area of minimal error (optimum performance) occurring at the lower control sensitivities of 1 through 8. A most interesting difference between Helson's results and those of the present study is the larger variation in error performance for changes in control sensitvity obtained in the former.

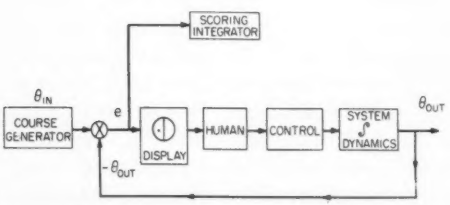


Fig. 1. Experimental first-order system containing a single integrator in the system dynamics which produces a velocity of cursor movement proportional to control displacement.

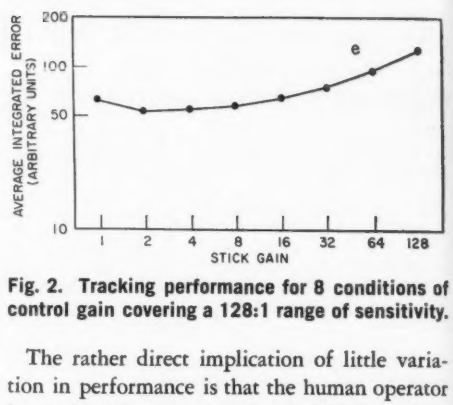


Fig. 2. Tracking performance for 8 conditions of control gain covering a 128:1 range of sensitivity.

The rather direct implication of little variation in performance is that the human operator is varying his own gain or sensitivity to compensate for variations in control sensitivity. In a purely mechanical system employing no human element, error is a direct function of system gain, which in turn is the product of the gain of each system component. Normally, a variation in the gain of a given system component would be reflected by a like variation in the error level. In the present case, however, a variation of 128 to 1 in the gain of the control component is reflected by only a 2.5 to 1 variation in the error level. One must conclude that the human system component is varying his own gain to maintain a given over-all system gain and thereby produce a nearly constant error performance. This capacity of the human to vary his gain is pointed out by Birmingham[1] who speculates that as a function of system characteristics this variation may range over as much as 100 db.

TABLE I

Statistical Significance of the Differences Between Conditions of Control Sensitivity

C_{ON_D}	1	2	4	8	16	32	64	128
1		25	31	28	25	15*	5*	0*
2			29	25	17*	10*	5*	0*
4				27	16*	7*	2*	0*
8					20*	10*	2*	0*
16						17*	3*	0*
32						.	9*	0*
64								8*

21 = .01 LEVEL*

Perfect compensation by the human operator of changes in control gain would, of course, produce a straight performance curve having zero slope. Such is the case for the lower control sensitivities. The accelerated form of the curve for the higher control sensitivities, however, does not reflect a serious failure to compensate, but rather a very small departure from perfect adjustment. As a matter of fact, the *maximum* error level was less than 1 percent of the course amplitude. In the system sense, then, the man-machine combination was accurate to within 1 percent of the input signal throughout the rather extensive range of control gain variation.

SUMMARY

A preponderance of studies have employed the positional type system in studying the various parameters of the tracking or control problem. An experiment was conducted to observe the effect of varying control sensitivity in a velocity control system. A single sine wave of 0.05 cps was used as the course input and the subjects tracked in the compensatory mode using a pressure control. The operator was required to apply a maximum force of 1 oz to stay on target when tracking with a maximum control gain, whereas 8 lb of force were required with a minimum control gain. Eight naval enlisted men received 8 test runs on 8 control sensitivities covering a range of 128 to 1. Test runs were 1 minute in length with the last 55 seconds being scored. The following results were obtained:

1. A region of minimum error or optimum performance occurred at the lower control sensitivities covering a range of 1 oz through 8 lb of required hand force. Fatigue was experienced, however, in the condition requiring 8 lb of force.

2. The over-all error variation was 2.5 times for the entire 128 to 1 range of control sensitivities.

3. The maximum average tracking error was calculated never to be more than 1 percent of the input amplitude.

It is concluded that the human operator compensates for changes in control sensitivity to produce an optimal performance over a wide range. Further, the similarity of these results and those obtained by Helson[5] suggests that the influence of control sensitivity is not materially different in zero and first-order systems.

REFERENCES

1. BIRMINGHAM, H. P. The optimization of man-machine control systems. Wescon Record, Part IV, 1958, *in press.*

2. CHERNIKOFF, R., and Taylor, F. V. Effects of course frequency and aided time constant on pursuit and compensatory tracking. *J. exp. Psychol.,* 1957, 53, 285-292.

3. HARTMAN, B. O. The effect of the extent of movement (control sensitivity) on pursuit tracking performance. U. S. Army Medical Research Laboratory Report 308, 1957.

4. HARTMAN, B. O., and FITTS, P. M. Relation of stimulus and response amplitude to tracking performance. *J. exp. Psychol.,* 1955, 49, 82-92.

5. Helson, H. Design of equipment and optimal human operation. *Amer. J. Psychol.,* 1949, 62, 473-497.

6. HELSON, H., and HOWE, W. H. Handwheel speed and accuracy of tracking. OSRD Rep. 3543, The Foxboro Co., 1943 (PB 40615).

7. JENKINS, W. L., and CONNOR, M. B. Some design factors in making settings on a linear scale. *J. appl. Psychol.,* 1949, 33, 359-409.

8. SEARLE, L. V., and TAYLOR, F. V. Studies of tracking behavior. I. Rate and time characteristics of simple corrective movements. *J. exp. Psychol.,* 1948, 38, 615-631.

9. WILCOXON, R. Some rapid approximate statistical procedures. Stamford, Conn.: American Cyanamid Co., 1949.

Optical System Design and the "Empty Field"[1]

MARTIN I. KURKE, Dunlap and Associates, Inc., Washington 4, D.C.

An experiment was performed to explore equipment design parameters for overcoming the accommodation disturbances in untextured visual fields which have been observed at high altitudes, and which have been reproduced under laboratory conditions. Under controlled field conditions, however, the phenomenon could not be elicited.

INTRODUCTION

Recent investigations at high altitude and in the laboratory have disclosed a phenomenon known as "empty field myopia." As described by Whiteside,[5] it consists in the main of an involuntary increase in the power of accommodation when searching in a visual field in which there is no detail sufficiently sharp to constitute a stimulus for the accommodation mechanism. The searcher then becomes virtually myopic and often cannot detect objects of small apparent sizes. However, Marano[4] points out that the effect on the visual system is in reality a loss of the ability to accommodate the eyes to various depths, and suggests the term "empty field myopia" should not be used to describe this condition. Whiteside's monograph devotes considerable space to studies for determining some of the parameters of this phenomenon. Brown[1] attempted to determine whether the design of equipment such as gunsight reticles could correct this defect but obtained negative results. He suggests that individual differences play a part in susceptibility to "empty field myopia" and that selection of pilots may have to take this factor into account.

The present study was designed to determine whether the accommodation disturbance in an "empty field" is sufficiently great to be considered in the design of ground-based optical search systems. Such systems would be required to search the sky at low elevations where terrain in the lower portion of the field provides texture, and therefore a depth of field gradient useful in depth perception (Gibson[3]), providing cues for accommodation. These systems would also be required to search at elevations at which the entire field consists of uniform cloud cover, or clear cloudless sky. Under such conditions, all the usual cues required for depth perception would not be present. That the design of equipment may be a significant parameter is suggested by Whiteside's conclusion that more than 2× magnification is required to detect a threshold size object when it is presented in an empty field. Brown interprets the results of earlier work (Campbell[2]) to mean that the correction of "empty field myopia" might be expected to double the range of detection under conditions where this phenomenon is likely to occur.

An experiment was therefore designed to determine whether Whiteside's laboratory results pertain to field conditions. His underlying assumption remained unchanged: the presence of "empty field myopia" will be indicated if the visual size threshold is greater in a textured than in an untextured field.

For the type of equipment under consideration, a minimum design specification could be established as a function of the magnifications in which no difference in threshold occurs as a function of the absence of field texture.

The present study investigated six ground-based search systems to determine significant parameters for the control of the differential

[1]The data reported here were collected while the author was at U. S. Army Ordnance Human Engineering Laboratory, Aberdeen Proving Ground, Md., and are partially reported within a technical memorandum of limited circulation.

effect of textured vs. "empty fields" as background for targets of minimal size.

APPARATUS AND PROCEDURE

Four optical systems were made available for this study. Two were low power military telescopes, one of 1×, the other 3×. Also used were two identical variable power rifle telescopes, one set at 2.5× and one at 3×. The two 3× scopes differed in objective lens diameter, width of field, and of course, the exit pupil. Also used was an empty tube with approximately the same field of view as the 1× telescope. Unrestricted binocular vision was also used as a control condition.

The target consisted of a set of thirteen 60° equilateral cones with a black matte finish. The cones ranged in size from ¼ in. to 3 in. in base diameter. Targets were presented individually in ascending size order and were suspended by a 0.11 in. monofilament line, invisible when viewed with 6 power binoculars at the test distance of 100 yards.

For half of the trials the optical systems were elevated so that only the sky formed a background. During the balance of the trials the scopes were trained so that both sky and terrain features were in the field of view. The targets were raised to predetermined heights to insure that they were near the center of the field, and in the textured background condition were high enough to insure that sky rather than trees were immediately behind them. Because the unrestricted binocular condition required an unbounded field of view, it was not possible to provide an empty field control condition for this condition. All the data were collected during one day. The sky was untextured by cloud formations. The sun was at the right and rear of the subjects so that sun glare would not affect visibility. The black matte finish on the target prevented detection from reflection.

Six non-astigmatic enlisted men were used as subjects. Their depth perception was normal and their visual acuities lay between 20/17 and 20/22 (Snellen) as measured by the Bausch & Lomb Orthorater. The optics and the open tube were mounted in five individual booths, and a separate booth was provided for unaided binocular vision. The booths were equipped with a shutter which provided 15-second tachistoscopic observations.

Scoring was done with pencil and paper; the subject placed an "X" by the appropriate presentation number if he saw the target and an "O" if he did not. Each subject was given 13 presentations for each background condition and each optical situation (all conditions for each subject). In each trial the subjects were first presented the 3-in. diameter cone as a target in the general area where they might expect the subsequent test targets.

The data were collected according to a repeated measures schedule and were analyzed according to analysis of variance technique designed to eliminate the effects of subject interaction.

RESULTS

The threshold data were subjected to Bartlett's Test and found to be homogeneous. An analysis of variance (summarized in Table I) yielded statistically significant differences between optics and between subjects. However, differences in backgrounds did not contribute to differences in thresholds.

DISCUSSION AND CONCLUSION

As was to be expected, both individual differences and differences in optical parameters influenced the threshold. The failure of background differences to elicit differential thresholds was not expected, and would seem to imply that factors other than an untextured field enter into the problem. The only known variable, visual ability, was controlled by using subjects with normal far vision and depth perception, and free from astigmatism. Glare, which might have been present in the laboratory or at high altitudes, was virtually absent in this experiment, but there is not enough evidence to determine whether this is an important contributing factor to the induction of the accommodation disturbance in empty fields.

TABLE I

Summary Analysis of Variance

Source	df	MS	F	
a) Between Optical Systems	5	2.842	34.78**	(a/e)
b) Between Backgrounds	1	0.014	< 1	(b/f)
c) Between Subjects	5	0.730	7.31*	(c/g)
d) Interaction: O x B	5	0.090	< 1	(d/g)
e) O x S	25	0.082	< 1	(e/g)
f) B x S	5	0.075	< 1	(f/g)
g) O x B x S	25	0.099		
TOTAL	71			

*Significance beyond .05 level

**Significance beyond .01 level

The present experiment was performed to explore equipment design parameters for overcoming the accommodation disturbances in untextured visual fields which have been observed at high altitudes and which have been reproduced under laboratory conditions. No disturbances comparable to those obtained in the laboratory or at a high altitude could be elicited under ground-based controlled field conditions. It may therefore be concluded that the need for developing additional design specifications to overcome the effects of the phenomenon in the ground-based optical search equipments under consideration cannot be justified.

REFERENCES

1. BROWN, R. H. 'Empty-field' myopia and visibility of distant objects at high altitudes. *Amer. J. Psychol.*, 1957, **70**, 376-385.

2. CAMPBELL, F. W. The depth of field of the human eye. RAF Flying Pers. Res. Comm. Rep. No. 868, Mar. 1954.

3. GIBSON, J. W. *The Perception of the Visual World.* Boston: Houghton-Mifflin, 1950.

4. MARANO, J. A. Myopia and accommodation. *Human Factors*, 1958, **1**, 46.

5. WHITESIDE, T. C. D. *The Problems of Vision in Flight at High Altitude.* London: Butterworths, 1957.

The Authors

BLAINE H. LEVEDAHL (*A Survey of Radiobiology for Engineers*) is an Associate Professor of Zoology at the University of California, Los Angeles, and a Consultant to the commercial aircraft division of the Douglas Aircraft Company, Inc., Santa Monica. He obtained his B.S. degree in chemistry at Brigham Young University in 1941 and his Ph.D. in biochemistry at the University of Utah in 1949. In the interim he worked for four years on internal ballistic problems at the California Institute of Technology for the Bureau of Ordnance, USN. After a year as a post-doctoral AEC Fellow in physical chemistry at Princeton (1950) Dr. Levedahl joined the staff at UCLA. Since 1955 he has worked as a consultant with Stanley Lippert and his group at the Douglas Aircraft Company in Santa Monica.

DR. LEVEDAHL is an editor of the symposium *"Radiation Biology at the Intra-Cellular Level,"* Pergamon Press (1959), and is a member of the Organization Committee for the Second Catalina Conference on Radiation Biology to be held in 1959. He is a member of the American Association for the Advancement of Science, The Biophysical Society, Society for Experimental Biology and Medicine, The Society of Western Naturalists, Sigma Xi, Sigma Pi Sigma (Physics), and the Human Factors Society. He is also on the Editorial Board of this journal.

MARTIN I. KURKE (*Optical System Design and the "Empty Field"*) is presently a human factors scientist at the Washington office of Dunlap and Associates, Inc., where he does work in human engineering, operations research and personnel research on several projects. From 1954 to 1957 he was a member of the Systems Evaluation Branch, U. S. Army Ordnance, Human Engineering Laboratory, Aberdeen Proving Ground, Maryland. Prior to that Mr. Kurke was employed as an applied experimental psychologist in the Operational Analysis and the Training Equipment Design groups at Bell Aircraft Corporation, Buffalo, N. Y.

MR. KURKE was born in Brooklyn, N. Y., and received his B.A. in psychology and biology from New York University in 1949. In 1953 he received the M.A. in experimental psychology at The University of Buffalo where he subsequently took some work in industrial engineering. He has completed his course work toward the Ph.D. in social and industrial psychology at American University. Mr. Kurke is a member of the American Association for the Advancement of Science, the American Ordnance Association, the American Psychological Association, the Ergonomics Research Society, the Human Factors Society, and the Society of Engineering Psychologists.

CLARENCE L. TIPTON and **HENRY P. BIRMINGHAM** (*The Influence of Control Gain in a First-Order Man-Machine Control System*).

CLARENCE L. TIPTON is an engineering psychologist and graduate of the George Washington University. He has been active in basic and applied research at the U. S. Naval Research Laboratory since 1946. As a member of the Operational Research Branch, Applied Research Division, he is currently employed in the development and operational analysis of the space surveillance system recently instituted by the U. S. Naval Research Laboratory.

HENRY P. BIRMINGHAM is head of the Human Engineering Development Section of the U. S. Naval Research Laboratory. He joined the Laboratory in 1945. In 1954 he received the U. S. Navy Meritorious Civilian Service Award for the "development of a basic human engineering theory relating to man-operated continuous control systems".

Born in Newburgh, New York, he received the Bachelor of Education degree in 1942 from the Rhode Island College of Education, and has

since done graduate work at the University of Pennsylvania and at the American University. He served as an instructor in radar maintenance and as a clasification specialist during World War II. He later joined the research staff of Brown University under NDRC and received the Navy Bureau of Ordnance Development Award for work in fire control.

Mr. Birmingham is a senior member of the Institute of Radio Engineers, and is chairman of the newly-formed IRE Professional Group on Human Factors in Electronics. He is also a member of the American and Eastern Psychological Associations.

EDITORIAL

MIRROR, MIRROR ON THE WALL

Our Society is now pressing toward the 500 member mark. We are proud of the achievement. Our geographical representation has expanded throughout the United States and into Australia, Canada, and Britain. The educational and work histories of our membership reflect the diverse backgrounds necessary to our multidisciplinary tasks. We are approaching the end of our second year as a national organization. Let us take an uncompromising and critical look at ourselves.

In education, no standard curriculum defines the substantive content of the field. Human factors is a bandwagon ridden by engineering departments, psychology departments, and schools of medicine.

In an interdisciplinary field such as ours, there are opportunities to play off one discipline against another. An unsuspecting engineering specialist may get a lot of fancy talk from us. With a skillful presentation of such talk he may be led to accept a unidiscipline solution to a problem requiring a multidiscipline approach. Is a little knowledge a lot of knowledge to a novice? Does an authoritarian manner in this new field pass for a real knowledge and understanding of the novel and provocative problems with a biological flavor which are our daily fare?

We can sell human factors. But are we to be only salesmen? In the Twenties, the efficiency experts sold hard, and some of the products were good. But they were the first to be fired when matters of bread and butter intervened. Have we fallen into the same trap, or have we been saved by degrees—advanced academic degrees?

In the future, will our work stand upon its own merits, or will it continue to rest on mandatory requirements of governmental agencies?

The demand for human factors specialists exceeds the supply. Salaries are excellent. Society members are job jumping in a lively fashion. Yet how much new knowledge do we bring to our assignments? Our major efforts appear to lie in selling the human factors approach to a problem, and then rehashing once again the tried and tired literature. We earn a living from this. But a contract cancellation can turn us into the equivalent of itinerant fruit pickers, looking for seasonal work where other plums are ripening.

We believe in ourselves and in our work. We want to be sincere and forthright. Yet we are faced with a real dilemma. We must sell our programs. Simultaneously, we must establish sound professional approaches in difficult problem areas. Through our personal contacts with government, industry, or educational institutions, we have entered upon a membership career in the Human Factors Society for our mutual benefiit.

The adjustments in the years ahead may be profound. As we busily prescribe principles for man-machine systems, we must not forget our larger ethical relationships in a man-social system. Our professional status in human factors is not a license to quackery. We must encourage honesty and dignity in our young profession so that we can always turn and ask without fear "Mirror, mirror on the wall..."

—John Lyman and Stanley Lippert

EXCELLENT OPPORTUNITIES FOR

PSYCHOLOGISTS

You are invited to investigate unusual career opportunities with excellent futures in the science and engineering Laboratories of IBM. You will find this to be a unique opportunity to contribute original thinking on several important projects.

Our Laboratories are engaged in the research and development of advanced electronic digital computers for business, science and industry. We are also engaged in the design of control systems for exotic-fueled strategic bombers to operate at altitudes of 70,000 feet and at speeds of more than 2,000 miles per hour.

- To undertake design, research, experimental analysis, and consultation in the field of man-machine relationships in a newly organized psychology group. Unusual opportunities for display and systems design in the early development stage. Projects include work in psychophysics, communications, electronics, trouble-shooting techniques, human learning, perception, operations analysis, high-speed data processing, psychometrics, information theory, decision processes, visual and auditory displays, and equipment design. Program includes both applied and basic experimentation. An advanced degree is required, or considerable experience in appropriate fields.

- To conduct systems analysis on complex, advanced weapons systems. A strong background in mathematics and statistics is desirable. An M.A. or Ph.D. in Psychology is required with experience in human engineering and human factors research.

- To initiate human factors design on Navy programs. Experience either on naval systems or equipment is highly desirable. An M.A. or Ph.D. in experimental psychology is required.

- To perform equipment evaluation experimentation, laboratory simulation, and flight test analysis from the human factors standpoint. An M.A. or Ph.D. in Psychology is required plus applied experimental experience.

- PERSONNEL AND TRAINING PSYCHOLOGIST to conduct maintenance and handling task-equipment analysis and other personnel analyses on advanced electronic systems. Knowledge of Air Force skill classifications and technical training and related equipment is desirable. Must have knowledge of airborne weapons system research and development cycle. An M.A. or Ph.D. in Psychology is required with specialization in industrial and engineering applications of psychological knowledge and techniques.

• • •

Salary commensurate with experience. Advancement based on merit. Employee benefits are among the best in industry today.

Please write, including resume, to:

Mr. R. E. Rodgers, Dept. 700H
International Business Machines Corp.
590 Madison Avenue
New York 22, N. Y.

IBM®

INTERNATIONAL BUSINESS
MACHINES CORPORATION